Genetische Analysen im Kontext der personalisierten Medizin: Ökonomische Betrachtungen zu Einsatz, Kosten, Faktoren, Strukturen und Implikationen in Deutschland

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Meinen Eltern

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Zusammenfassung

Genetische Diagnostik stellt eine Erweiterung des diagnostischen Leistungsspektrums dar und schafft die Grundlage, individuelle genetische Informationen in das Behandlungsmanagement eines Patienten zu integrieren. Aus dem molekulargenetischen Profil eines Patienten können diagnostische, prognostische und prädiktive Informationen generiert werden, welche z. B. Informationen zu Diagnose, Erkrankungsverlauf, Überlebens- und Erkrankungswahrscheinlichkeiten und Therapieerfolg liefern. Neben patientenrelevanten Vorteilen können genetische Analysen beispielsweise durch die Vermeidung von im Einzelfall nicht ausreichend wirksamen Therapien zu einer besseren Ressourcenallokation im Gesundheitswesen beitragen. Aufgrund des erheblichen Einsatzpotentials, sind genetische Analysen bereits heute aus einer Vielzahl von Indikationsgebieten nicht mehr wegzudenken und sowohl die humangenetische Forschung als auch der technologische Fortschritt führen zu einer stetigen Ausweitung der Applikationsmöglichkeiten. Die vorliegende Dissertation beschäftigt sich mit zentralen Fragestellungen in den Bereichen Struktur, Kosten, Einsatz, Faktoren und Implikationen von genetischer Diagnostik im deutschen Versorgungssetting.

Diese kumulative Dissertation setzt sich aus neun Publikationen zusammen. Gesundheitsökonomische Analysen in Bezug auf die Kostendimension umfassen dabei eine Kostenanalyse der Ganzgenomsequenzierung, Budget-Impact-Analysen zum Einsatz von Ganzgenomsequenzierungen in der Onkologie und beim genetischen Neugeborenenscreening, eine Routinedatenanalyse zur Evaluation der Versorgungskosten des Mammakarzinoms als auch ein systematisches Review zur Kosteneffektivität von pharmakogenetischen Tests. Die Publikation zum Einsatz von individualisierter Medizin verdeutlicht das Versorgungs- bzw. Einsatzpotential von genetischer Diagnostik in der Onkologie. Versorgungsstrukturelle Betrachtungen werden in zwei weiteren Publikationen adressiert. Zum einen werden ökonomische Rahmenbedingen im Hinblick auf das prädiktive Potential umfassender genetischer Analysen diskutiert und definiert. Zum anderen werden aufgrund der steigenden Komplexität der Diagnosestellung humangenetische Beratungsstrukturen einer Kapazitätsanalyse unterzogen. In einem Discrete-Choice-Experiment werden die Einflussfaktoren auf die Durchführung einer Ganzgenomsequenzierung bzw. die Präferenzen zur Ausgestaltung eines solchen genetischen Tests untersucht. Außerhalb der qualitätsgesicherten Versorgung stellen genetische Direct-to-Consumer Tests über das Internet eine weitere Zugangsmöglichkeit zu genetischen Analysen dar. In einer systematischen Anbieterrecherche werden neben dem aktuell verfügbaren Angebot die potentiellen Implikationen von internetbasierten genetischen Analysen in einem solidarisch-finanzierten Gesundheitssystem betrachtet.

Genetische Analysen sind das zentrale Werkzeug der personalisierten Medizin – ein Markt der durch eine große Entwicklungsdynamik gekennzeichnet ist. Das wachsende genetische Wissen führt zu

einer stetigen Ausweitung von Applikationsmöglichkeiten und Anwendungsgebieten. Es bedarf sowohl gesundheitsökonomischer Evaluationen, um die neuen Einsatzpotentiale valider Kosten- und Nutzenbetrachtungen zu unterziehen als auch der Betrachtung der Versorgungsforschung im Hinblick auf strukturelle und prozessuale Adaptionen.

Schlagwörter: Genetische Diagnostik, Ganzgenomsequenzierung, personalisierte Medizin, individualisierte Medizin, Neugeborenenscreening, Onkologie, Humangenetische Beratungen, Versorgungsforschung

Abstract

Genetic testing is an extension of diagnostic spectrum and provides a basis to integrate individual genetic information into the patient's treatment management. The molecular genetic profile of patients provides diagnostic, prognostic and predictive information for diagnosis, disease progression, probabilities of disease, surveillance and therapeutic success. In addition to patient-relevant benefits, genetic testing may lead to a better allocation of resources in the healthcare system, for example, by avoidance of ineffective therapies. Due to considerable potential of genetic applications, genetic testing today is already indispensable in a large number of indications. The human genetic research as well as technological progress have been contributing to an ongoing expansion of possible applications. The present doctorate thesis addresses central issues of genetic testing in terms of structure, cost, application, factors and implications for the German healthcare system.

This cumulative dissertation constitutes of nine publications. Health economic analysis regarding to the costs comprises a cost analysis of whole genome sequencing, budget-impact analyses for the use of whole genome sequencing in oncology and newborn screening, a claims data analysis of the costs of breast cancer as well as a systematic review of the cost-effectiveness of pharmacogenetics tests. The publication on the use of individualized medicine illustrates the potential of genetic testing for application in oncology healthcare. Two further publications address corresponding issues in healthcare structure. Economic framework with respect to the predictive potential of comprehensive genetic testing are discussed and defined. Due to the increasing complexity of genetic testing in the diagnostic process, an analysis of capacity of human genetic counselling structures is performed. A discrete-choice experiment evaluates the influencing factors for the execution of whole genome sequencing. Outside of quality-assured care, direct-to-consumer genetic testing via the Internet provides a further access possibility to the genetic analysis. In a systematic provider research, the current available supply is evaluated and the potential implications of internet-based genetic analysis for a solidary financed healthcare system are discussed.

The genetic testing is the central tool of personalized medicine – a market characterized by a great development potential. Growing genetic knowledge leads to an increasing extension of application possibilities and application areas. Health economic evaluations are necessary to evaluate the costs and benefits of new applications and review the current healthcare structures and processes for possible adjustments.

Key words: genetic diagnostic, whole genome sequencing, personalized medicine, individualized medicine, newborn screening, oncology, human genetic counselling, health care research

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1 Motivation und Zielsetzungen

1.1 Genetische Diagnostik als Grundlage neuer medizinischer Versorgungskonzepte

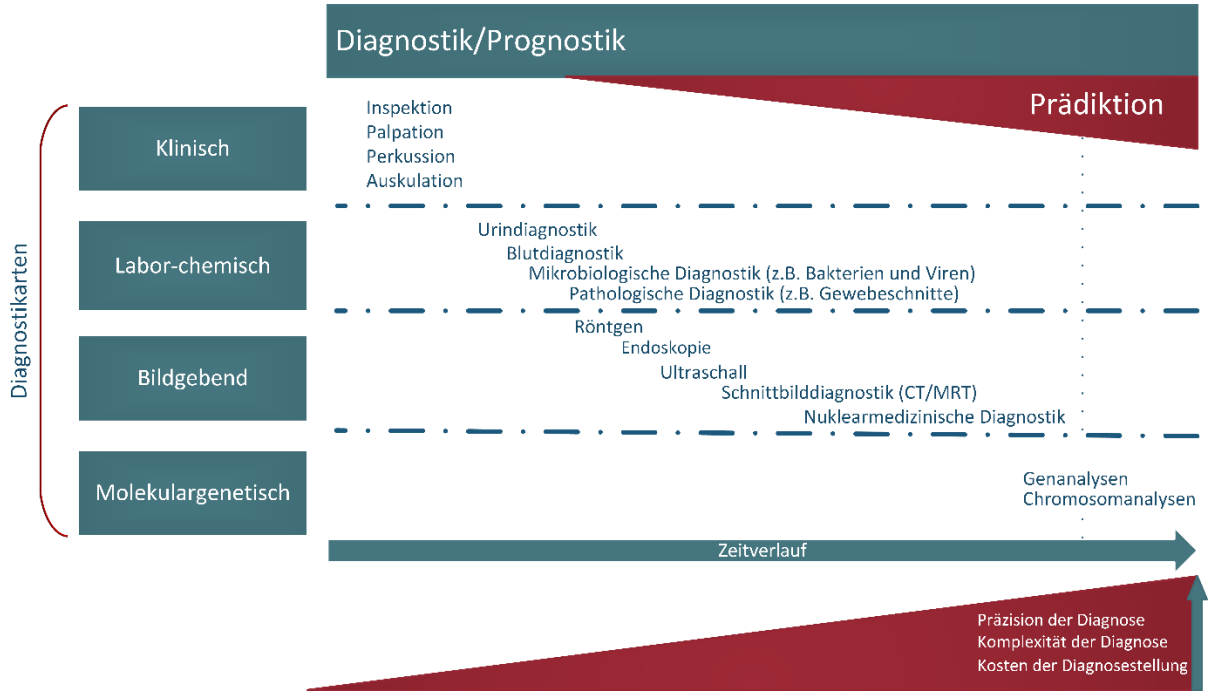
Personalisierte Produktempfehlungen, nach dem individuellen Geschmack zusammengestellte Nahrungsmittel und personalisierte Verpackungen sind nur einige Lebensbereiche, in welchen die Personalisierung bereits Einzug gehalten hat. Dieser Trend lässt sich auch in der medizinischen Versorgung beobachten.

„Individualisierte Medizin“, „Personalisierte Medizin“, „Stratifizierte Medizin“ und „Präzisionsmedizin“ sind nur einige Begriffe für Versorgungskonzepte, die mit dem Trend der Personalisierung der Medizin in Zusammenhang gebracht werden. Während die „Stratifizierung“ in der Medizin primär die Medikamentenapplikation auf Basis genetischer Biomarker, „personalisierte Medizin“ die Behandlung genetisch-ähnlicher Patientenkohorten und „Präzisionsmedizin“ die passende Therapie für einen spezifischen Patienten zu einem bestimmten Zeitpunkt beschreibt, ist „individualisierte Medizin“ durch den höchsten Individualisierungsgrad, beispielsweise durch maßgeschneiderte Therapien in Form von patientenindividuell hergestellten Tumorvakzinen, gekennzeichnet. Diese Begriffe finden, unabhängig von unterschiedlichen Graden der Individualisierung, häufig eine synonyme Verwendung [1-2]. Trotz der Begriffsvielfalt bzw. den unterschiedlichen Anwendungsschwerpunkten sind dies alles Behandlungskonzepte, die auf einem gemeinsamen Nenner fußen: Der genetischen Diagnostik bzw. Analyse im Vorfeld von Behandlung und Therapie. Durch genetische Analysen werden Möglichkeiten geschaffen, versorgungsrelevante Entscheidungen (Auswahl von Arzneimitteln, Präventionsmaßnahmen aufgrund von genetischen Dispositionen etc.) auf Grundlage des genetischen Profils eines Patienten treffen zu können [2]. Eine beinahe Verdopplung des weltweiten Umsatzes von 890 Mrd. US-Dollar in 2012 auf 1.590 Mrd. US-Dollar in 2017 zeigt nicht nur die Relevanz, sondern auch die Entwicklungsdynamik des Marktes für personalisierte Medizin [3].

1.1.1 Erweiterung des diagnostischen Spektrums durch genetische Analysen

Ein Blick in die Medizingeschichte zeigt, dass sich Mediziner schon seit der Antike verschiedener Diagnostika bedienten, um basierend auf diesen Diagnosen zu objektivieren und Therapieentscheidungen initiieren zu können. Inzwischen kann auf eine Vielzahl unterschiedlicher Diagnostika zurückgegriffen werden, welche sich von der klassischen klinischen Diagnostik, der Laboratoriumsmedizin über die bildgebende Diagnostik bis hin zur molekulargenetischen Diagnostik erstrecken (siehe Abbildung 1).

Abbildung 1: Erweiterung des diagnostischen Leistungsspektrums



Quelle: Eigene Darstellung

Diagnostika können in drei wesentlichen Kontexten Informationen liefern [4-5]:

(1) diagnostisch (Identifikation, Klassifikation oder Früherkennung von Krankheiten),

(2) prognostisch (potentielle Heilungschancen und Verlauf von Erkrankungen),

(3) prädiktiv (Wahrscheinlichkeit der Penetranz für bestimmte Krankheiten und/oder die Wahrscheinlichkeit des Ansprechens auf bestimmte Therapien).

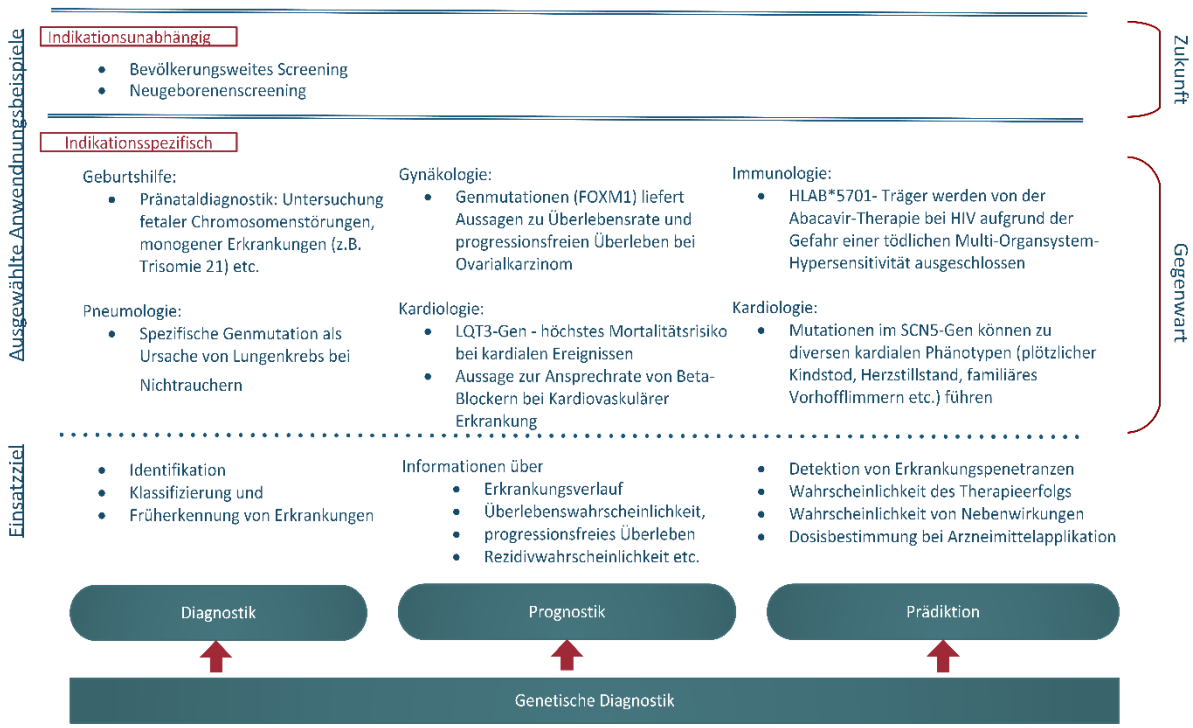
Während weiterführende Diagnostika bis vor einigen Jahren primär auf die diagnostische und prognostische Abklärung klinisch erhobener Befunde abzielten, ermöglicht es die molekulargenetische Diagnostik Befunde auch in einem rein prädiktiven Kontext zu generieren. In der Detektion von Erkrankungsdispositionen im Vorfeld einer Manifestation wird das entscheidend neue Potential der genetischen Diagnostik gesehen. Genetische Biomarker, wie genetische Mutationen oder Genprodukte, dienen den behandelnden Ärzten neben der individuellen Krankheitsgeschichte, Laborparametern (Zellen, Stoffwechselprodukte, Enzyme und Hormone), Mikrobiologie, Pathohistologie und/oder bildgebender Diagnostik als eine Erweiterung bestehender diagnostischer Parameter. Zur Objektivierung der Bewertung werden genetische Biomarker als Messgröße herangezogen und können sowohl Auskunft über biologische und pathologische Prozesse als auch Aussagen über das Ansprechverhalten von pharmakologischen, präventiven und sonstigen Gesundheitsinterventionen liefern [5-6].

Genetische Diagnostik eröffnet den Akteuren neue Möglichkeiten in der Versorgung. Gleichbedeutend geht dies jedoch auch mit einer Zunahme der Komplexität und somit auch der Kosten der Diagnosestellung aufgrund aufwendiger Analyseinterpretationen einher. Diese erreichen im postgenomischen Zeitalter, seit der Entschlüsselung des menschlichen Genoms, durch die Berücksichtigung von Interaktionsbeziehungen zwischen Genen und Umweltbedingungen (Ernährung, Verhaltensweisen etc.) neue Dimensionen [7].

1.1.2 Genetische Diagnostik als zentraler Grundstein der medizinischen Versorgung

Molekulargenetische Diagnostik schafft die Grundlage individuelle genetische Informationen in das Behandlungsmanagement von Patienten zu integrieren. Genetische Informationen können u.a. zur Diagnosefindung bei seltenen oder schwer zu diagnostizierenden Erkrankungen oder zur Initiierung von Therapieentscheidungen herangezogen werden. Aufgrund des erheblichen Einsatzpotentials sind genetische Analysen in einer Vielzahl von Indikationsgebieten der aktuellen medizinischen Versorgung nicht mehr wegzudenken und nehmen bereits heute eine Schlüsselrolle bei diversen Therapieentscheidungen ein (siehe Abbildung 2).

Abbildung 2: Ausgewählte Anwendungsgebiete von genetischer Diagnostik



Quelle: eigene Darstellung auf Basis von [1, 4, 8-11]

Grundsätzlich kann genetische Diagnostik je nach Fragestellung zwischen indikationsunabhängigen und indikationsspezifischen Anwendungen differenziert werden. Indikationsspezifische Analysen finden z. B. in der Ermittlung des individuellen Brustkrebsrisikos durch den Nachweis von BRCA I/ BRCA II Anwendung. Hingegen eröffnen sich im prädiktiven Kontext neue Möglichkeiten des genetischen Screenings von asymptomatischen und somit phänotypisch-gesunden Personen, wie bspw. im Rahmen des genetischen Neugeborenenscreenings. Während genetische Screenings in der aktuellen Versorgung bis dato eher eine untergeordnete Rolle spielen, sind pharmakogenetische Anwendungen bereits in einer Vielzahl von Indikationen durch einen hohen Verbreitungsgrad gekennzeichnet. Genetisch-diagnostische Tests detektieren bestimmte erkrankungsrelevante Mutationen oder spezifische Enzymkonstellationen, die nicht nur zu einer Unterteilung bzw. Stratifizierung des Patientenkollektives beitragen, sondern auch Informationen über Aufnahme, Verteilung, Abbau oder Ausscheidung von spezifischen Arzneimitteln für das jeweilige Kollektiv geben können [12]. Grundsätzlich können genetische Tests im Vorfeld der Medikamentenapplikation folgende Informationen liefern [12-13]:

- Wirksamkeit eines spezifischen Wirkstoffes,
- Bestimmung und Anpassung der Dosis und/oder
- Aussagen zur Therapiesicherheit.

Neben patientenrelevanten Vorteilen (Erhöhung der Gesamtüberlebensrate, Reduktion von Nebenwirkungen, Verbesserung von Lebensqualität und/oder Ansprechraten auf spezifische Therapien etc.) können genetische Wirksamkeitstests auf Systemebene bspw. unwirksame Therapien vermeiden, Folgekosten reduzieren und somit letztlich zu einer besseren Ressourcenallokation im Gesundheitswesen beitragen [14].

1.2 Versorgungsrelevante Aspekte und Implikationen für die Forschung

Humangenetische Forschung bildet die Grundlage der vielfältigen Applikationen genetischer Diagnostik. Um phänotypischen Krankheitsausprägungen evidente genotypische Auffälligkeiten zuordnen zu können, bedarf es einer großen Menge an genetischen und pathologischen Daten. Genomweite Assoziationsstudien (GWAS) stellen hierfür ein essentielles Instrument dar, um aus Phänotyp-Genotyp-Korrelationen versorgungsrelevante Informationen zu generieren [15-16]. Neben den technologischen Voraussetzungen (Sequenzierungstechnologien, genetische Datenbanken, Analyseinstrumenten etc.) bedarf es jedoch zunächst der Bereitschaft der betroffenen Patienten, die persönlichen genetischen Daten der Forschung zur Verfügung zu stellen. Genetische Analysen können in zwei wesentlichen Dimensionen Nutzen generieren: Auf der einen Seite können Patienten unmittelbar durch die Steigerung der Behandlungsqualität, bspw. in Form von schnelleren Diagnosen oder

der Vermeidung von Nebenwirkungen, profitieren. Auf der anderen Seite könnten durch die Bereitstellung der persönlichen genetischen Daten für Forschungsaktivitäten perspektivisch positive externe Effekte für Dritte generiert werden [17-18].

Nutzendebatten über genetische Analysen haben im Kontext der Forschung einen gänzlich anderen Fokus als im Versorgungskontext. Während im Rahmen von Forschungsaktivitäten die Etablierung einer breiten Datenbasis im Vordergrund steht, stellen spezifische genetische Informationen im klinischen Kontext einen wesentlichen Aspekt einer effizienten und effektiven Versorgung dar. Im Vorfeld einer Implementierung ins diagnostische Leistungsspektrum der gesetzlichen Krankenversicherung (GKV) bedarf es für Erstattungsentscheidungen zu Lasten der Solidargemeinschaft neben Nutzennachweisen ebenfalls valider Kostenevaluationen. Im Zusammenhang mit dem prädiktiven Potential genetischer Analysen mangelt es zum aktuellen Zeitpunkt oftmals nicht nur an Nutzennachweisen oder verfügbaren Behandlungsmöglichkeiten, sondern auch an Regelungen hinsichtlich offener ethischer, rechtlicher und ökonomischer Fragestellungen.

Ungeachtet der Nutzendebatten, lässt sich mit zunehmendem Wissen über den Einfluss genetischer Faktoren auf die Erkrankungsmanifestierung auch ein wachsendes Interesse für genetische Analysen in der Bevölkerung beobachten [19]. Außerhalb des qualitätsgesicherten Versorgungssettings stellen genetische Analysen über das Internet (sogenannte genetische Direct-to-Consumer-Tests (DTC-Tests)) für Selbstzahler eine vermeintlich kostengünstigere Alternative dar. Die Vor- und Nachteile von genetischen Analysen sind jedoch für den Konsumenten allein nur schwer bis gar nicht zu beurteilen, was durch die Implementierung des Gendiagnostikgesetzes (GenDG) im Jahr 2010 und der damit definierten obligatorischen Beratung im Rahmen prädiktiver genetischer Analysen unterstrichen wurde. Während Patienten im klassischen Versorgungssetting dieser Beratung verpflichtend unterliegen, kann im internetbasierten Markt einer Einhaltung dieser Reglementierung häufig nicht zur Gänze Rechnung getragen werden und birgt somit die Gefahr, dass Folgekosten (z. B. aufgrund von Verunsicherung oder Erkrankungsangst durch probabilistische Befunde) zu Lasten der Solidargemeinschaft entstehen können.

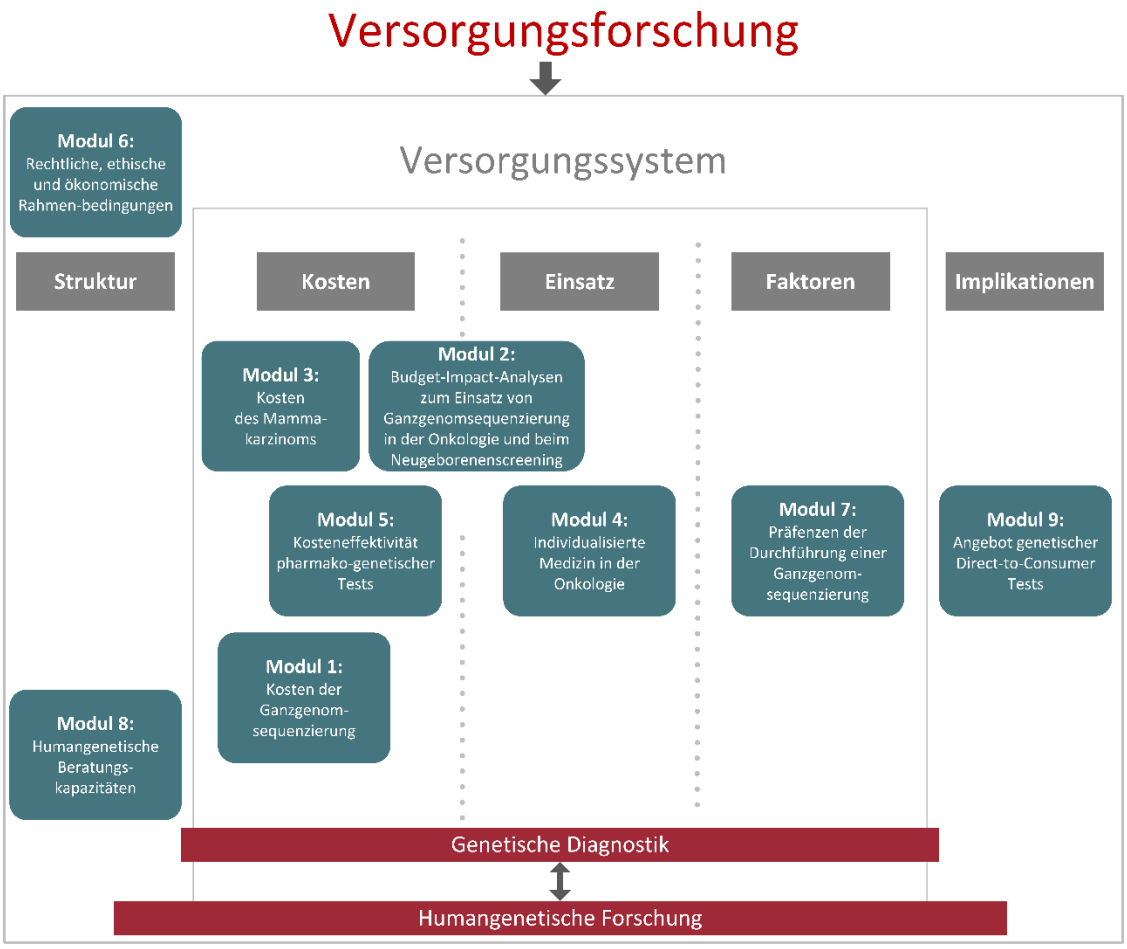
Je nach Umfang der genetischen Analyse variieren nicht nur der Aufwand des Diagnostikprozesses und die Komplexität der humangenetischen Beratung. Auch die Menge an genetischen Daten stellt die Mediziner in Punkto Dateninterpretation vor Herausforderungen. Im Zuge der stetig fortschreitenden genetischen Erkenntnisse, wie bspw. epigenetischen Faktoren, stehen die Akteure vor der Herausforderung diesen gewachsenen Ansprüchen innerhalb der aktuellen Versorgungsstrukturen gerecht zu werden.

Die vorliegende kumulative Dissertation hat die Beantwortung der folgenden zentralen Fragestellungen zum Gegenstand:

1. Wie hoch sind die Kosten einer Ganzgenomsequenzierung im qualitätsgesicherten deutschen Versorgungssetting und welche Kosten entstehen durch den Einsatz in ausgewählten Anwendungsgebieten?
2. Führt die Applikation eines vorherigen genetischen Wirksamkeitstests im Bereich der Pharmakotherapie zu kosteneffektiven Anwendungen und welche Kriterien beeinflussen hierbei die Kosteneffektivität?
3. In welchem Indikationsgebiet sind pharmakogenetische Applikationen am häufigsten vertreten und welche Kosten entstehen in dieser Indikation im Rahmen der Standardversorgung?
4. Unter welchen Bedingungen ist die deutsche Bevölkerung bereit eine Ganzgenomsequenzierung durchführen zu lassen?
5. Sind Adaptionen bestehender Versorgungsstrukturen aufgrund umfassender genetischer Analysen notwendig?
6. Auf welches Angebot an genetischen Tests kann die deutsche Bevölkerung über das Internet zugreifen und welche potentiellen Implikationen entstehen durch diese im Gesundheitssystem?

Die Beantwortung der vorliegenden Fragestellungen liefert der Versorgungsforschung wichtige Einblicke in den Bereichen Struktur, Kosten, Einsatz, Faktoren und Implikationen von genetischer Diagnostik im deutschen Setting (siehe Abbildung 3).

Abbildung 3: Modulübersicht



Quelle: eigene Darstellung

2 Beitrag der vorliegenden kumulativen Dissertationsarbeit

2.1 Kosten und Einsatz von genetischer Diagnostik

2.1.1 Ganzgenomsequenzierung – Kosten und ökonomische Auswirkungen

Der zentrale Grundstein der heutigen genetischen Analysemöglichkeiten wurde durch die Initiierung des Human Genome Projects im Jahr 1990 gelegt. Ein Konsortium aus internationalen Wissenschaftlern publizierte im Jahr 2000 die Ergebnisse der Entschlüsselung des humanen Genoms [20]. Die Entschlüsselung des ersten humanen Genoms mittels der Sequenzierung nach Sanger verursachte Kosten in Höhe von ca. 3 Mrd. € [21]. Die Kettenabbruchmethode nach Sanger ist eine der klassischen Methoden der DNA-Sequenzierung und wird heutzutage weiterhin als Goldstandard zur Validierung auffälliger Befunde herangezogen [22]. Technologische Fortschritte und Entwicklungen haben den Bereich der Sequenzierungstechnologien im letzten Jahrzehnt wesentlich geprägt. Die Ver-

fahren der nächsten Generation (engl. next generation sequencing), welche aufgrund der parallelen Sequenzierung zu erheblichen Zeit- und Kostenreduktionen führten, haben sich auf dem Markt etabliert und befinden sich bereits in der vierten Entwicklungsgeneration [23]. Während bspw. im Jahr 2001 die Sequenzierung einer Mega-Base[1] ca. $5.292 kostete, reduzierten sich diese Kosten in 2017 auf $0,012 pro Mega-Base. Dies entspricht im Hinblick auf die Sequenzierung eines humanen Genoms einer Kostenreduktion von $95.263.072 auf $1.121 [24].

Die Entscheidung über den Umfang der genetischen Analyse wird durch die initiale Fragestellung bestimmt und beeinflusst demzufolge neben dem Umfang bzw. der Sequenzierungsbreite auch die Analysekosten. Je nach Untersuchungsziel können die behandelnden Akteure zwischen folgenden Analysearten wählen:

Tabelle 1: Arten genetischer Analysen

Analyseart	Analyseumfang
Einzelgen-Analyse	Mutationsanalyse eines spezifischen Gens
Gen-Panel-Analyse	Analyse von Gen-Panels, welche mit bestimmten Krankheiten oder pharmakogenetischen Wirkungen assoziiert werden; Gen-Panels umfassen eine Vielzahl an krankheits-assoziierten Genen
Ganzexom-Analyse (engl. Whole Exome Sequencing (WES))	Sequenzierung der proteinkodierenden Abschnitte des Genoms (entspricht 1-2 % des Genoms)
Ganzgenomsequenzierung (engl. Whole Genome Sequencing (WGS))	Sequenzierung des gesamten Genoms

Quelle: eigene Darstellung in Anlehnung an [25-26]

Mit einer Sequenzierung von ca. 3 Milliarden Basenpaaren ist die Ganzgenomsequenzierung [21] (engl. Whole Genome Sequencing (WGS)) die umfangreichste und demzufolge auch kostenintensivste genetische Analyse. Die Durchführung einer WGS erfordert im klinischen und ambulanten Setting eine Einbettung in einen qualitätsgesicherten Prozessablauf. Prozessschritte, wie bspw. genetische Beratungen und Dateninterpretation haben dabei einen wesentlichen Einfluss auf die Gesamtkosten. Aus diesem Grund evaluiert die in **Modul 1** eingebrachte Publikation „Cost Analysis of Whole Genome Sequencing in German Clinical Practice“ die Durchführungskosten einer WGS unter Sicherstellung eines qualitätsgesicherten Prozessablaufs in der deutschen Versorgung.

[1] Genetische Informationen werden in Nukleinbasen gespeichert. Eine Mega-Base entspricht dabei einer Million Nukleinbasen.

Der zentrale Ausgangspunkt für diese Kostenevaluation war die Abbildung eines qualitätsgesicherten WGS-Prozesses am Deutschen Krebsforschungszentrum in Heidelberg. Die Kosten einer WGS werden erheblich von der eingesetzten Technologie (Investitions- und Wartungskosten, Materialkosten, Dauer und Anzahl der Genome pro Sequenzierungsdurchlauf etc.) beeinflusst. Aus diesem Grund wurden die Kosten der derzeit in Deutschland vorherrschenden Technologie HiSeq 2500 der Firma Illumina, Inc. mit der neusten Sequenzierungsplattform HiSeq Xten von Illumina, Inc. verglichen. Durch den Einsatz der HiSeq Xten könnten die Kosten um etwa 65 % von ca. 3.876 € auf ca. 1.379 € pro Genom reduziert werden. Allerdings divergieren die Investitionskosten der beiden Plattformen erheblich. Während die Anschaffungskosten der HiSeq 2500 bei 667.000 € liegen, belaufen sich die Investitionskosten für die HiSeq Xten auf 8,8 Mio €. Als zentraler Kostenfaktor der Sequenzierung mittels der aktuellen Standardtechnologie konnten die Materialkosten mit etwa 2.845 € pro Genom ermittelt werden. Weiterhin haben Faktoren, wie die Auslastung der Sequenzierungsplattform und die Coverage, welche die Abdeckung bzw. die Häufigkeit der Sequenzierung einer Gensequenz bezeichnet, einen entscheidenden Einfluss auf die Kostenkalkulation. Wie sich die Veränderung einer dieser beiden Faktoren auf das vorab definierte Base-Case-Szenario (Auslastung der Plattform von 80 % und 30-fache Coverage) auswirkt, konnte mittels Sensitivitätsanalysen simuliert werden. Differenzen in der Auslastung, bspw. durch Ausfälle, Reinigungen oder Wartungen, wirken sich nur gering auf die Material-, Anschaffungs- und Wartungskosten aus. Hingegen hat eine Veränderung der Coverage einen erheblichen Einfluss auf die Kostenhöhe. Eine Erhöhung der Coverage bspw. von einer 30-fachen auf eine 75-fache Abdeckung, mit dem Ziel genauere Analyseergebnisse zu erreichen, führt zu einem Anstieg der Material-, Anschaffungs- und Wartungskosten von 3.455 € auf 8.596 €. Die Entscheidung vom derzeit geltenden Goldstandard (30-fache Coverage) abzuweichen, hängt u.a. von Faktoren, wie der Expertise des Arztes, der Spezifität der Fragestellung und dem Analyseumfang ab. Während die Kosten des Prä-Sequenzierungs- (z. B. humangenetische Beratung und Blut- bzw. Gewebeentnahme) und Sequenzierungsprozesses (z. B. DNA-Extraktion und Reinigung des Sequenzers) exakt zu quantifizieren und monetär zu bewerten sind, divergieren die Positionen des Postsequenzierungs-Prozesses (Datenanalyse, -interpretation und -validierung) erheblich mit dem jeweiligen Analysefall und wurden somit aus der Analyse exkludiert. Es kann jedoch angenommen werden, dass diese einen erheblichen Einfluss auf die Kostenhöhe haben.

Im Vorfeld der Implementierung von neuen Technologien und therapeutischen oder präventiven Interventionen bedarf es valider Kostenanalysen, um die hierdurch entstehenden Kosten für die Solidargemeinschaft abschätzen zu können. Die durchgeführte Kostenanalyse kann als Ausgangsbasis für weiterführende Kostenkalkulationen des Einsatzes von WGS in der Versorgung herangezogen werden. Hierbei dienen u.a. Budget-Impact-Analysen als Instrument, um die potentiell anfallenden Kosten für bestimmte Patientengruppen oder Indikationsgebiete zu prognostizieren und basierend auf

diesen Erstattungsentscheidungen zu treffen. In **Modul 2** analysiert die Publikation „Ganzgenomsequenzierung in der deutschen Versorgung – Ökonomische Auswirkungen eines Einsatzes in ausgewählten Anwendungsgebieten“ die Kosten eines potentiellen Einsatzes von WGS im Rahmen des genetischen Neugeborenenscreenings und der genetischen Analyse des gesamten onkologischen Patientenkollektives.

Der Einsatz von WGS im Rahmen des genetischen Neugeborenenscreenings stellt ein indikationsunabhängiges Einsatzgebiet dar. Asymptomatische Neugeborene werden einer genetischen Analyse unterzogen, um bis dato unbekannte Dispositionen zu detektieren bzw. identifizieren. Basierend auf den Daten des statistischen Bundesamtes wurden die Kosten für den Einsatz von WGS bei allen Neugeborenen (n=737.575) im Jahr 2015 kalkuliert. Ein Einsatz hätte Durchführungskosten von 2,85 Mrd. € verursacht, was einen Anteil von 1,41 % der GKV-Leistungsausgaben entsprochen hätte. Eine frühzeitige Detektion von Keimbahnmutationen ermöglicht es, präventive und therapeutische Maßnahmen im Vorfeld einer Erkrankungsmanifestation zu initiieren, um einen möglichen Krankheitsausbruch zu verhindern oder die Schwere des Krankheitsverlaufs zu reduzieren. Neben diesen Nutzendebatten, werden aber auch Bedenken bezüglich indikationsunabhängiger genetischer Analysen laut. Die zum aktuellen Zeitpunkt oftmals noch fehlenden Behandlungsmöglichkeiten für probabilistische Befunde als auch das Risiko, durch genetische Informationen gesunde Kranke zu schaffen, die aus Angst ihre Nachfrage nach Gesundheitsleistungen steigern könnten, sind Aspekte, welche die Forderung genetische Analysen an spezifische Indikationen zu binden, unterstreichen.

An diese Forderung knüpft die Kostenkalkulation für ein indikationsbezogenes Einsatzszenario im onkologischen Setting an. Eine genomweite Analyse aller Tumorpatienten hätte im Jahr 2015 Kosten in Höhe von 0,84 Mrd. € verursacht, was einen Anteil von 0,42 % an den Leistungsausgaben der GKV entsprochen hätte. Zudem wurden differenzierte Kalkulationen für die zehn häufigsten onkologischen Indikationen durchgeführt. Der Einsatz von WGS beim Mammakarzinom, welches mit einer Fallzahl von 17.444 die häufigste Tumorerkrankung bei Frauen ist, hätte bspw. im Jahr 2015 Kosten von ca. 63,4 Mio. € verursacht. Hierbei handelt es sich lediglich um eine Betrachtung bereits Erkrankter. Eine additive Berücksichtigung der Sequenzierung von Risikopatienten würde zu Kostensteigerungen führen. Um jedoch eine Aussage darüber treffen zu können, inwieweit sich derart umfangreiche genetische Analysen auf die Kosten innerhalb der Indikation des Mammakarzinoms auswirken, bedarf es valider Erhebungen der aktuellen Versorgungskosten.

2.1.2 Evaluation der Versorgungskosten des Mammakarzinoms

An den Bedarf der Evaluation der aktuellen Versorgungskosten am Beispiel der häufigsten onkologischen Indikation bei Frauen schließt die in **Modul 3** eingebrachte Publikation „Healthcare costs

associated with breast cancer in Germany – a claims data analysis“ an. In dieser Analyse werden die direkten Kosten des Mammakarzinoms in der deutschen Versorgung für verschiedene Behandlungsphasen (initial, intermediär und terminal) aus der Perspektive der Gesetzlichen Krankenversicherung evaluiert. Auf Grundlage einer Routinedatenanalyse der Abrechnungsdaten der AOK Bayern wurden die versorgungsrelevanten Kosten, wie ambulante und stationäre Kosten, Arzneimittel, Heil- und Hilfsmittel, Rehabilitation, Krankengeld und Fahrkosten, für die Jahre 2011-2014 erfasst. Grundlage ist eine Studienpopulation von 36.033 weiblichen Mammakarzinom-Patientinnen, von denen 28.522 prävalente und 4.185 inzidente Brustkrebs-Fälle darstellen. Das durchschnittliche Alter beträgt 67,32 [SD=12,23] Jahre. Im Betrachtungszeitraum befanden sich 3.954 Patientinnen in der Initialphase, 28.838 in der intermediären Phase und 2.416 in der terminalen Phase. Die mit Abstand höchsten inkrementellen Kosten pro Patientin in Höhe von 21.386 € zeigen sich in den ersten elf Monaten nach Diagnose in der Initialphase. In der intermediären Phase liegen die inkrementellen Jahreskosten je Patientin bei 2.866 € (inzident) bzw. 2.426 € (prävalent). Obwohl sich die Kosten in den letzten sechs Monaten vor dem Tod in der Interventionsgruppe auf 21.011 € (inzident) bzw. 20.226 € (prävalent) pro erkranktem Versicherten belaufen, liegt das Inkrement im Vergleich zur Kontrollgruppe bei 2.421 € (inzident) bzw. 1.557 € (prävalent) pro Patientin. Weiterhin konnte evaluiert werden, dass die Kosten in den meisten Phasen mit steigendem Alter sinken. Die Kosten für Zytostatika und teilweise auch die stationären Kosten, hatten einen wesentlichen Einfluss auf die Kostenhöhe der jeweiligen Behandlungsphase.

Der Einsatz von genetischen Analysen zur Spezifizierung von Diagnosen oder zur Objektivierung von Therapieentscheidungen erfolgt vorwiegend zu Beginn einer Erkrankung. Demzufolge würde sich der Einsatz von genetischen Analysen primär kostensteigernd in der Initialphase auswirken. Genetische Analysen im Rahmen von personalisierten Arzneimittelapplikationen, können jedoch auch in den anderen Behandlungsphasen zu Kostensteigerungen führen oder durch zeitnahe Therapieinterventionen eine Reduktionen von Folgekosten ermöglichen. Ob personalisierte Arzneimittelapplikationen in der Indikation des Mammakarzinoms bereits Anwendung finden, wurde in der nachfolgend dargestellten Studie untersucht.

2.1.3 Personalisierte Therapien – Applikationsgebiete und Kosteneffektivität

Die in **Modul 4** eingebrachte Publikation „Individualisierte Medizin bei ausgewählten Krebserkrankungen“ veranschaulicht, dass im Untersuchungsjahr 2016 elf der 42 in Deutschland zur personalisierten Medizin zugelassenen Wirkstoffe für die Behandlung des Mammakarzinoms eingesetzt wurden. Durch personalisierte Therapien können innerhalb dieser Indikation neben Outcome-Verbesserungen (längeres progressionsfreies Überleben, besseres Therapieansprechen etc.) u.a. auch Verbesserungen der Lebensqualität und/oder Erhöhung der Gesamtüberlebenszeit erzielt wer-

den. Ein ähnliches Bild ergibt sich für das nicht-kleinzelligen Lungenkarzinom (NSCLC), der häufigsten Tumorerkrankung bei Männern. Anfang des Jahres 2016 waren für NSCLC fünf Wirkstoffe zur personalisierten Medikamentenapplikation zugelassen.

Indikationen mit hohen Versorgungskosten, wie am Beispiel der Kostenanalyse zum Mammakarzinom aufgezeigt wurde, hohen Prävalenz– und Sterblichkeitsraten oder schlechten therapeutischen Outcomes können erheblich durch die Anwendung von personalisierten Therapien profitieren. Derartige Parameter sind kennzeichnend für das onkologische Setting. Krebserkrankungen sind nach Herz-Kreislauf-Erkrankungen die zweithäufigste Todesursache in Deutschland [27] und verursachten bspw. im Jahr 2015 Krankheitskosten in Höhe von ca. 19,9 Mrd. € [28]. Mit der Entwicklung von genetischen Tests wurde die Möglichkeit geschaffen, die Therapie des Patienten anhand seines genetischen Profils effizient zu steuern und somit die Versorgungskosten nachhaltig zu beeinflussen.

Neben der Nutzenevaluation von patientenrelevanten Outcomes im Rahmen von klinischen Studien, sind aufgrund des Kostendrucks im Gesundheitswesen ökonomische Evaluationen notwendig, um das Kosten-Nutzen-Verhältnis von pharmakogenetischen Medikamentenapplikationen abschätzen zu können. Ob genetische Tests zu einer effizienteren Versorgung oder zu Kosteneinsparungen führen, ist Gegenstand von Kosten-Nutzen- oder Kosten-Effektivitäts-Analysen. Die in **Modul 5** eingebrachte Publikation “Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies-A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany” untersucht die Effektivität der in Deutschland im Rahmen der personalisierten Medizin zugelassenen genetischen Tests.

Ziel des Reviews war die Evaluation des Einflusses der zur Steuerung der medikamentösen Therapien zugelassenen genetischen Tests auf die Kosteneffektivität der Medikamentenapplikation. In das systematische Review wurden somit ausschließlich Studien eingeschlossen, die den Einsatz eines personalisierten Wirkstoffes ohne vorherigen Wirksamkeitstest mit der Wirkstoffverabreichung mit vorherigem genetischen Test vergleichen. Zum Untersuchungszeitpunkt im Jahr 2016 waren 47 Wirkstoffe zur personalisierten Therapie zugelassen. Für 39 von diesen war ein vorheriger genetischer Test verpflichtend und für acht empfohlen.

27 Studien konnten anhand der Einschlusskriterien in die finale Übersicht eingeschlossen werden. Eine Vielzahl der Studien (n=12) untersucht die Anwendung eines genetischen Tests in einer onkologischen Indikation (z. B. Darmkrebs und Brustkrebs im Frühstadium), gefolgt von Studien bei immunologischen Erkrankungen (n=7) (chronisch-entzündliche Darmerkrankungen, rheumatologische Erkrankungen etc.), HIV/Aids (n=5) und Epilepsie (n=3). Die am häufigsten untersuchte Medikamentenapplikation erfolgte für den Wirkstoff Azathioprin in immunologischen Indikationen, wie chro-

nisch-entzündlichen Darmerkrankungen, rheumatologischen Erkrankungen, idiopathische Lungenfibrose und Autoimmunerkrankungen. Weiterhin wurde identifiziert, dass die meisten Evaluationen für die Biomarker-Analyse von Thiopurin-Methyltransferase (TMPT) durchgeführt wurden. Um eine Aussage über die Qualität der Studien treffen zu können, wurden diese einer qualitativen Bewertung mittels des Quality of Health Economic Studies (QHES)- Instrument [29] unterzogen. Alle eingeschlossenen Studien erreichten im Durchschnitt eine gute Qualität (85,81 von 100 Punkten), wobei Studien im Publikationszeitraum zwischen 2009-2015 eine höhere Qualität erzielten als Studien, die zwischen 2002 und 2008 publiziert wurden.

Als weitere wesentliche Ergebnisse des Reviews konnten identifiziert werden, dass

- in der Mehrzahl der eingeschlossenen Studien die Medikamentenapplikation mit einem vorherigen pharmakogenetischen Tests zu Kosteneinsparungen führt bzw. kosteneffektiv ist,
- keine grundsätzliche Aussage darüber getroffen werden kann, ob genetische Tests (unabhängig von der Indikation) zu einer kosteneffektiven Applikation führen und
- sich die Kosteneffektivität eines personalisierten Wirkstoffs nicht nur zwischen den Indikationen, sondern auch innerhalb der einzelnen Indikationsgebiete unterscheidet.

Kosten-Effektivität-Analysen zielen darauf ab, Verbesserungen die durch Innovationen im Vergleich zur bisherigen Standardtherapie erreicht werden können, abzubilden. Die Kosten-Effektivität einer medizinischen Intervention hängt demnach davon ab, ob Vorteile zur Standardtherapie zu angemessenen Kosten generiert werden können. Methodische und konzeptionelle Aspekte, wie (1) Wahl der Perspektive (Gesellschaft, Krankenversicherung etc.), (2) Zeithorizont und Diskontierung, (3) Sensitivität und Spezifität der genetischen Testverfahren, (4) Prävalenz der Biomarker, (5) Testkosten, (6) Prävalenz der Nebenwirkungen und Ansprechraten auf die Therapien, (7) Kosteneffektivitätsschwellen und (8) Mangel an evidenz-basierten Studien haben, wie ebenfalls im Review identifiziert werden konnte, einen direkten Einfluss auf das Evaluationsergebnis. Um eine Vergleichbarkeit der Evaluationen von stratifizierten Arzneimitteln sicherzustellen, sollten verbindliche nationale und internationale Standards definiert werden.

2.2 Genetische Analysen – Faktoren, Strukturen und Implikationen

Während genetische Analysen im Bereich der personalisierten Pharmakotherapie bereits zur aktuellen Versorgung zählen, befinden sich umfassendere genetische Analysen, wie Exomsequenzierungen (engl. Whole Exome Sequencing (WES)) und WGS, noch am Anfang einer breiten klinischen Anwendung. In Verbindung mit umfassenden genetischen Analysen treten eine Vielzahl an Fragestellungen bezüglich des prädiktiven Potentials auf. In der in **Modul 6** eingebrachten Publikation „Genomanaly-

sen als Informationseingriff – Ethische, juristische und ökonomische Analysen zum prädiktiven Potential der Ganzgenomsequenzierung“ wurden umfassende Überlegungen und Lösungen zur Überführung prädiktiver genetischer Analysen in die Regelversorgung adressiert. Hierbei wurden neben ethischen und rechtlichen Überlegungen und Handlungsempfehlungen, wie bspw. zum Umgang mit Zusatzbefunden und der Gestaltung von genetischen Beratungen, vor allem auch notwendige versorgungsrelevante Aspekte definiert. Zentrale gesundheitsökonomische Ziele waren dabei die Abbildung des Status Quo (Potentiale und Risiken prädiktiver Analysen aus ökonomischer Perspektive, Finanzierungsmöglichkeiten und Abrechnungsmodalitäten, Kostenevaluation, Versicherungsfähigkeit hinsichtlich genetischer Risikoprofile, Wettbewerbsfähigkeit im nationalen und internationalen Marktgeschehen etc.) als auch die Generierung von Handlungsempfehlungen zum Umgang mit prädiktiven genetischen Analysen im Versorgungskontext. Dabei wurden u.a. die Notwendigkeit der Einführung einer Prädiktionsdiagnose als neue Diagnoseart, welche zugleich auch die Voraussetzung zur Initiierung weiterführender Maßnahmen schafft, die Definition von prädikationsspezifischen Schwellenwerten, Indikationsbegrenzungen als auch Zentralisierungsempfehlungen der Durchführung und der Definition von Qualitätskriterien für umfassende genetische Analysen diskutiert und definiert.

Grundsätzlich ist die Wahl des Analyseumfangs (Einzelgenanalyse, Panelsequenzierung, WES oder WGS) von der spezifischen Fragestellung abhängig. Während Einzelgenanalysen zielfokussierter sind und die klinische Relevanz einer genetischen Mutation durch die behandelnden Ärzte unmittelbar in den Erkrankungskontext eingeordnet werden kann, bedarf es bei umfassenderen Analysen aufwendigerer Ergebnisinterpretationen. Hierfür stellen bioinformatische Filter im klinischen Kontext ein essentielles Instrument dar, um die genetischen Informationen auf bekannte erkrankungsrelevante genetische Abweichungen zu untersuchen und reduzieren. Während in der Versorgung die Begrenzung der Analyseergebnisse zum Zweck einer schnelleren Interpretationsfähigkeit eine erhebliche Relevanz besitzt, sind in der humangenetischen Forschung umfassende genetische Informationen von großer Bedeutung. Ein umfassender genetischer Datenpool schafft die Voraussetzung, um durch Phänotyp-Genotyp-Korrelationen den Abweichungen vom Referenzgenom eine Erkrankungsrelevanz zuzuordnen. Aus diesem Grund gab es in den letzten Jahren eine Vielzahl an internationalen politischen Initiativen bzw. Programmen (z. B. 100.000 Genomes-Projekt in Großbritannien, Saudi Human Genome Program in Saudi Arabien), welche auf die Sequenzierung breiter Bevölkerungsteile abzielten, um für phänotypische Merkmalsausprägungen einen genotypischen Ursprung zu identifizieren [30].

Eine Grundvoraussetzung von humangenetischer Forschung ist nicht nur die Bereitschaft der Bevölkerung eine umfangreiche genetische Analyse durchführen zu lassen, sondern auch die Einwilligung,

die persönlichen genetischen Daten der Forschung zur Verfügung zu stellen. Aus diesem Grund untersucht die in **Modul 7** eingebrachte Publikation „Which attributes of whole genome sequencing tests are most important to the general population? Results from a German preference study", welche Aspekte eines WGS-Tests einen Einfluss auf die Durchführungsbereitschaft haben. Hierfür wurde ein Discrete-Choice-Experiment (DCE) durchgeführt, um die Präferenzen für die Durchführung einer WGS auf Basis einer Auswahl- und entscheidungsbasierten Analysemethode zu evaluieren. Bei einem DCE werden den Befragten zwei Wahlszenarien mit unterschiedlichen Testausprägungen gegenüber gestellt. Hieraus können durch Teilnutzwerte wichtige Eigenschaften bzw. Ausprägungen, die einen Einfluss auf die Auswahlentscheidung haben, bestimmt werden [31]. Die verschiedenen hypothetischen Testoptionen wurden aus den Attributen Testgenauigkeit, Testkosten, Ausbruchswahrscheinlichkeit der Erkrankung, Art der identifizierten Krankheit und Datenzugang zusammengestellt.

Die am meisten präferierte Ausgestaltung eines WGS-Tests in einer Kohorte von 301 Personen setzt sich aus folgenden Attributen zusammen: (1) Testgenauigkeit von 95 %, (2) Rückmeldung von schweren Erberkrankungen, (3) Rückmeldung von Befunden ab einer 40%igen Ausbruchswahrscheinlichkeit, (4) Testkosten von 1000 € und (5) Zugang der persönlichen Daten für Forschungszwecke. Die Möglichkeit, die persönlichen Daten der genetischen Forschung zur Verfügung zu stellen, hatte dabei einen positiven Einfluss auf die Durchführungsbereitschaft für eine WGS. Als ein wesentliches Studienergebnis konnte somit das Bewusstsein bezüglich der Relevanz genetischer Forschung in der Bevölkerung abgeleitet werden. Neben der grundsätzlichen Bereitschaft der Partizipation an der genetischen Forschung, konnte ebenfalls die Notwendigkeit von genetischen Beratungen aus den Ergebnissen gefolgert werden. Die „Testgenauigkeit" und die „Rückmeldung von Befunden ab einer bestimmten Krankheitsausbruchswahrscheinlichkeit" können einen essentiellen Einfluss auf das Leben des Getesteten haben. Im DCE wurden bei diesen Attributen die intermediären Level präferiert, wobei hierbei angenommen werden kann, dass mit einer vorherigen genetischen Beratung dem Attribut „Testgenauigkeit" und der „Wahrscheinlichkeit des Krankheitsausbruchs" vermutlich ein höheres Gewicht beigemessen worden wäre. Für einen Patienten oder Interessierten ist es kaum möglich, die Konsequenzen einer WGS abzuschätzen. Mit der Verabschiedung des GenDG wurden genetische Beratungen zu einem obligaten Bestandteil im Prozess von prädiktiven genetischen Analysen. Seither bedürfen prädiktive genetische Analysen einer umfassenden genetischen Beratung bzw. Aufklärung im Vorfeld als auch im Nachgang der Untersuchung. Genetische Beratungen sollen dazu beitragen, dass Chancen und Risiken im Zusammenhang mit prädiktiven Analysen für die Patienten selbst als auch für deren Familienmitglieder abzuschätzen sind.

Die Durchführung von humangenetischen Beratungen wurde zunächst auf die Facharztgruppe der Humangenetiker beschränkt. Im Zuge der vermehrten Applikationsmöglichkeiten genetischer Analy-

sen, wurde die Möglichkeit von fachgebundenen genetischen Beratungen geschaffen. In diesem Regelungsbereich sind allerdings umfassende indikationsunabhängige genetische Analysen, wie WES und WGS, nicht inbegriffen. Aus diesem Grund untersucht die in **Modul 8** eingebrachte Publikation „Humangenetische Beratungen im Rahmen prädiktiver genetischer Diagnostik – Eine Analyse der verfügbaren Kapazitäten im deutschen Setting“, inwieweit die aktuell vorherrschenden Strukturen einen wachsenden Bedarf an genetischen Beratungen Rechnung tragen können. Für die Kapazitätsanalyse wurden 135 ambulant und 55 stationär tätige Fachärzte für Humangenetik in die Kalkulation eingeschlossen. Basierend auf Annahmen zum Anteil der Beratungsstunden an der Arbeitszeit (80 % im ambulanten und 40 % im stationären Setting), einer Arbeitszeit von 42 Stunden/Woche und einer mittleren Beratungsdauer von 1,75 Stunden für die zwei obligatorischen genetischen Beratungen, ergibt sich aufgrund der Begrenzung der Beratungskapazitäten eine jährlich mögliche Fallzahl von 143.520 umfassenden prädiktiven genetischen Analysen. Aufgrund der Restriktion der Beratungskapazitäten könnten somit lediglich 19 % der 737.575 Neugeborenen oder 0,17 % der Gesamtbevölkerung im Jahr 2015 einer WGS, unter Sicherstellung der notwendigen verpflichtenden Beratung, unterzogen werden. Der stetig steigenden Nachfrage an genetischen Analysen als auch der aufgrund des wachsenden genetischen Wissens zunehmenden Komplexität der Beratung, steht eine zahlenmäßig kleine Anzahl der zur genetischen Beratung befugten Ärzte gegenüber [32]. Mittelfristig ist es eine Aufgabe des Gesetzgebers durch strukturelle Anpassungen, wie bspw. der Ausweitung des zur Beratung befugten Personenkreises, einem potentiell drohenden Defizit an genetischen Beratungskapazitäten entgegen zu wirken.

Unabhängig von der Frage der Notwendigkeit des Arztvorbehaltes ist die Tatsache, dass qualifizierte humangenetische Beratungen im prädiktiven Kontext zwingend erforderlich sind. Der zum Schutz des Patienten notwendige Aufklärungs-, Einwilligungs- und Beratungsprozess kann im ambulanten und stationären Setting durch gesetzliche Regelungen sichergestellt werden. Außerhalb der gesicherten Versorgungsrealität gestaltet sich diese Qualitätssicherung jedoch schwieriger. In den letzten Jahren hat sich neben der qualitätsgesicherten Versorgung ein zweiter Markt für genetische Analysen über das Internet entwickelt. Interessierte Personen, ohne medizinische Indikationsstellung und somit außerhalb des Regelungsbereichs des SGB V, stehen hierbei einem leicht zugänglichen aber vor allem auch häufig deutlich günstigeren Angebot gegenüber. Mit welchem Angebotsspektrum der Interessierte in einem stark regulierten Markt wie Deutschland konfrontiert ist und welchen Einfluss genetische DTC-Analysen in einem solidarisch-finanzierten Gesundheitssystem haben können, untersucht die in **Modul 9** eingebrachte Publikation „Health-Related Genetic Direct-to-Consumer-Tests in the German Setting: The Available Offer and the Potential Implications for a Solidary Financed Health-Care System“.

Die Marktanalyse wurde mittels einer systematischen Internetrecherche durchgeführt. Der Fokus der Analyse lag hierbei auf den gesundheitsbezogenen genetischen DTC-Tests, die sich in Lifestyle-Analysen (Ernährung, Gewicht etc.), prädiktive (z. B. Test auf die Wahrscheinlichkeit Alzheimer zu entwickeln) und diagnostische (z. B. Mutationen die eine Lactoseintoleranz auslösen) Analysen differenzieren lassen. Um das Angebotsspektrum zu identifizieren, das sich direkt an die deutschen Verbraucher richtet, wurde eine Suchstrategie (bestehend aus 37 Suchanfragen) in deutscher Sprache entwickelt. Von zunächst 559 potentiell relevanten Internetseiten wurden nach der Prüfung der Ein- und Ausschlusskriterien 35 Internetseiten in die finale Übersicht eingeschlossen. Der Verbraucher kann auf ein internationales Angebot zugreifen, dessen Vergleichbarkeit durch nachfolgende Aspekte erschwert wird:

- Begriffspluralismus für die gleichen genetischen Analysen,
- Angebote für Einzelgen-Analysen oder Paket-Analysen (Analyseumfang umfasst bis zu 35 Krankheitsdispositionen) und/oder Geschlechts-spezifischen Analyseangeboten,
- erheblichen Preisdivergenzen (z. B. Kosten für Einzelgen-Analysen können zwischen 89 € (Test auf Thromboserisiko) und 990 € (Test auf Risiko für Stoffwechselerkrankungen) oder Paket-Analysen zwischen 232 (Test auf 34 Krankheitsdispositionen) und 375 € (Test auf das Risiko 28 bekannter Erkrankungen) variieren) und
- teils fehlenden Informationen bzgl. Preis, Zertifizierung, Anzahl der untersuchten Genvariationen, Sensitivität und Spezifität der Testverfahren und/oder Akkreditierung.

Genetische Analysen bergen sowohl Chancen als Risiken für die beteiligten Akteure (Patient, Arzt, Krankenversicherung und System) auf den unterschiedlichen Systemebenen. Während prädiktive oder diagnostische Analysen eine erhebliche Auswirkung auf das Leben des Getesteten haben können, wird genetischen Lifestyle-Analysen ein eher geringerer Einfluss beigemessen. Somit unterscheiden sich auch die Effektstärken sowohl positiver als auch negativer Natur auf die GKV-Ausgaben. Die negativen Effekte (Angst, Verunsicherung, gestiegener Beratungsaufwand, erneute diagnostische Abklärungen, nachfrageinduziertes Angebot) stellen eine potentielle Gefahr einer unzureichenden oder fehlenden genetischen Beratung dar und können mit erheblichen Folgekosten einhergehen. Informationskampagnen könnten zur Stärkung des öffentlichen Bewusstseins und der Konsumentensouveränität beitragen. Somit könnten die mit den genetischen DTC-Tests einhergehenden Chancen und Risiken verdeutlicht und damit vor allem auch die negativ-assoziierten Effekte begrenzt werden.

3 Zusammenfassung der Ergebnisse und Ausblick auf den weiteren Forschungsbedarf

Genetische Diagnostik stellt bereits heute einen wichtigen Bestandteil in einer Vielzahl von Indikationsgebieten dar und könnte zukünftig als zentrale Ausgangbasis für jegliche Therapieentscheidungen und Diagnosepräzisierungen herangezogen werden. Der technische Fortschritt und die humangenetische Forschung tragen dabei zu einer stetigen Weiterentwicklung der Einsatzmöglichkeiten bei. Genetische Diagnostik an sich als auch die Ausweitung der Anwendungs- und Behandlungsmöglichkeiten bedürfen umfassender ökonomischer und versorgungsspezifischer Evaluationen. Mit der Beantwortung der nachfolgenden gesundheitsökonomischen Fragestellungen, konnte die vorliegende Dissertationsarbeit einen wesentlichen Beitrag für die Versorgungsforschung leisten:

1. *Wie hoch sind die Kosten einer Ganzgenomsequenzierung im qualitätsgesicherten deutschen Versorgungssetting und welche Kosten entstehen durch den Einsatz in ausgewählten Anwendungsgebieten?*

In der in Modul 1 durchgeführten Analyse konnten Durchführungskosten von 3.876 € pro WGS auf der derzeitig vorherrschenden Sequenzierungsplattform evaluiert werden. Einen entscheidenden Einfluss auf die Kostenhöhe haben neben der Auswahl der Sequenzierungstechnologie auch Annahmen zur Wahl der Coverage und Auslastung des Gerätes. Die Kostenanalyse zielte auf eine allgemeingültige Abbildung der Versorgungskosten ab, weshalb Kosten für die Datenanalyse, -interpretation und -validierung aufgrund der Fall- und Standortspezifität aus der Erhebung exkludiert wurden. Diesen Kostenfaktoren wird jedoch im Zusammenhang mit der Vorhaltung kostenintensiver IT-Infrastruktur und hohen personellen Zeitaufwendungen ein erheblicher Einfluss auf die Kostenhöhe beigemessen. Weiterführende Forschungsarbeiten könnten an diese Erhebung anschließen und den Einfluss dieser Prozessschritte auf die Gesamtkosten evaluieren.

Eine genomweite Analyse aller onkologischen Patienten hätte im Jahr 2015 Kosten in Höhe von 0,84 Mrd. € verursacht, was einem Anteil von 0,42 % an den Leistungsausgaben der GKV entsprochen hätte. Werden hingegen die Kosten des Einsatzes von WGS in indikationsunabhängigen Anwendungsgebieten, wie dem genetischen Neugeborenenscreening betrachtet, scheinen die Kosten zu Lasten der Solidargemeinschaft mit einem Ausgabenvolumen von 2,85 Mrd. € immens. Nach SGB V unterliegen Kostenerstattungsentscheidungen zudem der Notwendigkeit konkreter Nutzennachweise. Kostenerstattungen von WGS sind u.a. aufgrund der aktuell zum Teil noch fehlenden Behandlungsmöglichkeiten für Zufallsbefunde erschwert. Die Evaluation der Kosteneffektivität von umfassenden genetischen Analysen bspw. bei unklaren Diagnosen, könnte weiterer Gegenstand gesundheitsökonomischer Forschung sein.

2. *Führt die Applikation eines vorherigen genetischen Wirksamkeitstests im Bereich der Pharmakotherapie zu kosteneffektiven Anwendungen und welche Kriterien beeinflussen die Kosteneffektivität?*

In einer Vielzahl der in Modul 5 betrachteten Studien stellt ein genetischer Wirksamkeitstest im Vorfeld der Medikamentenapplikation ein wirksames Steuerungsinstrument dar, um eine kosteneffektive oder kostensparende personalisierte Arzneimittelverabreichung zu erzielen. Die Vergleichbarkeit der Studienergebnisse ist allerdings aufgrund fehlender nationaler und internationaler Standards hinsichtlich der Durchführung von Kosteneffektivitätsanalysen im Bereich der personalisierten Arzneimitteltherapie erschwert. Faktoren wie z. B. Studienperspektive, Zeithorizont, Diskontierung, Sensitivität und Spezifität der Testverfahren, Annahmen zur Biomarkerprävalenz, Testkosten und Datenqualität haben einen wesentlichen Einfluss auf das Evaluationsergebnis und bedürfen daher einheitlich definierter Standards. Nicht nur neue personalisierte Arzneimittel und genetische Wirksamkeitstests, sondern auch die Applikationsausweitung bzw. die Zulassung bekannter Wirkstoffe und Tests in neuen Indikationsgebieten erfordern stetige gesundheitsökonomische Evaluationen.

3. *In welchem Indikationsgebiet sind pharmakogenetische Applikationen am häufigsten vertreten und welche Kosten entstehen in dieser Indikation im Rahmen der Standardversorgung?*

In Indikationen, welche durch schlechte therapeutische Outcomes und hohe Versorgungskosten gekennzeichnet sind, besitzt der Einsatz von personalisierten Therapien ein großes Potential, Outcome-Verbesserungen zu angemessenen Kosten zu generieren. Kennzeichnend ist dies für das onkologische Setting. Die Mehrzahl der aktuell verfügbaren personalisierten Therapien sind in der Onkologie zugelassen, was das Versorgungspotential in onkologischen Indikationen unterstreicht. Für das Mammakarzinom, der häufigsten onkologischen Erkrankung bei Frauen, entstehen bspw. in den ersten elf Monaten nach der Diagnosestellung Versorgungskosten in Höhe von 21.386 € pro inzidenter Patientin. Weiterer Forschungsbedarf könnte in der Evaluation des Einflusses von zielgerichteten genetischen Analysen sowohl auf die kurzfristigen als auch langfristigen Versorgungskosten des Mammakarzinoms gesehen werden.

4. *Unter welchen Bedingungen ist die deutsche Bevölkerung bereit eine Ganzgenomsequenzierung durchführen zu lassen?*

Die am meisten präferierte Ausgestaltung eines WGS-Tests in der deutschen Bevölkerung setzt sich aus einer Testgenauigkeit von 95 %, der Rückmeldung von schweren Erberkrankungen, und dies ab einer 40 %igen Wahrscheinlichkeit eines Erkrankungsausbruchs, Testkosten von 1000 € und der Bereitstellung der persönlichen Daten für Forschungszwecke zusammen. Die Bereitstellung der eigenen genetischen Daten für Forschungszwecke war dabei ein Aspekt, der einen positiven Einfluss auf die

Bereitschaft zur Durchführung einer WGS hatte. Dies verdeutlicht das Bewusstsein der Studienteilnehmer hinsichtlich der Relevanz von humangenetischer Forschung. Eine Evaluation der Gründe hierfür (altruistisches Verhalten, Angst vor Erbkrankheiten, persönliche Krankheitsgeschichte etc.) als auch eine bevölkerungsweite Erhebung zum vorhandenen Wissen von genetischen Analysen in Forschung und Versorgung könnten an diese Studie anschließen. Die in Modul 7 dargestellte Präferenzerhebung zur Ausgestaltung eines WGS-Tests basiert zudem auf einer Entscheidungssituation ohne eine vorherige humangenetische Beratung. Eine vergleichende Präferenzerhebung hinsichtlich der Durchführungsentscheidung von WGS mit und ohne vorherige Beratung, könnte den Einfluss und die Relevanz von genetischen Beratungen in der deutschen Versorgung evaluieren.

5. *Sind Adaptionen bestehender Versorgungsstrukturen aufgrund umfassender genetischer Analysen notwendig?*

Eine Vielzahl der die Versorgungsstruktur-betreffenden Aspekte, wie Empfehlungen zur Einführung einer Prädiktionsdiagnose und prädiktionsspezifischen Schwellenwerten, der Erweiterung von Qualitätskriterien etc. erfordern im Falle einer breiten Implementierung von WGS in das Versorgungssetting einer verbindlichen Definition und Regelung. Umfassende genetische Analysen ohne einen konkreten Indikationsbezug erfordern aufgrund des prädiktiven Potentials qualifizierter humangenetischer Beratungen sowohl im Vorfeld als auch im Nachgang der Analyse. Sollten zukünftig umfassende genetische Analysen zu prädiktiven Zwecken in den Regelungsgegenstand des SGB V fallen, könnten Adaptionen humangenetischer Versorgungsstrukturen notwendig werden. Die Komplexität der Diagnosefindung und der Umfang des Beratungsaufwands steigen mit Zunahme des genetischen Wissens. In Anbetracht der potentiell zukünftig zu geringen humangenetischen Beratungskapazitäten könnten Diskussionen und Evaluationen zur Ausweitung des zur genetischen Beratung befugten Personenkreises und deren Einfluss auf das Versorgungssystem Gegenstand weiterer Forschungsvorhaben sein.

6. *Auf welches Angebot an genetischen Tests kann die deutsche Bevölkerung über das Internet zugreifen und welche potentiellen Implikationen entstehen durch diese im Gesundheitssystem?*

Der interessierte Konsument kann auf eine Vielzahl genetischer Analyseangebote über das Internet zugreifen. Die Angebote gesundheitsbezogener Analysen erstrecken sich von Lifestyle-Analysen bis hin zu diagnostischen und prädiktiven Untersuchungen. Hierbei ist der Verbraucher mit einem Angebot konfrontiert, das aufgrund von erheblichen Preisdivergenzen, verschieden ausgestalteten Angebotspaketen und teils fehlenden Informationen schwer vergleichbar ist. Das Internet ermöglicht den Konsumenten den Zugriff auf eine Vielzahl an internationalen Angeboten, die nicht den eigenen länderspezifischen Reglementierungen und Qualitätsstandards unterliegen. Dies birgt ne-

ben Chancen, wie der frühzeitigen Detektion von Erkrankungen und der damit verbundenen potentiellen Reduktion von Folgekosten, auch Risiken. Neben möglichen fehlerhaften Testergebnissen bergen zudem prädiktive Befunde, vor allem ohne vorherige Aufklärung und genetische Beratung, die Gefahr der Verunsicherung und Verängstigung des Getesteten. Potentielle Folgen können u.a. aufgrund eines nachfrageinduzierten Angebotes in einer Fehl- und Überversorgung durch Leistungsausweitungen oder des Aufweichens des Indikationsbegriffes gesehen werden. Weitere gesundheitsökonomische Forschungsvorhaben könnten die Evaluation der Leistungsinanspruchnahme aufgrund von prädiktiven Befunden, möglicherweise differenziert nach absoluten und relativen Risiken, zum Gegenstand haben.

Genetische Diagnostik als ein Instrument der Diagnosestellung und -präzisierung, Steuerung des Behandlungsmanagements und Therapieverlaufs als auch zur frühzeitigen Detektion von Penetranzen, ist bereits ein wichtiger Bestandteil unserer derzeitigen Versorgungslandschaft. Genetische Analysen sind in diesem dynamischen Feld der Innovationsmotor, welche die Grundlage für weitere Applikationsmöglichkeiten schaffen. Die Möglichkeit Behandlungsentscheidungen auf Basis genetischer Informationen zu treffen bedarf aufgrund des stetig wachsenden genetischen Wissens und der Ausweitung der Anwendungsgebiete struktureller Anpassungen in den Bereichen Lehre, Forschung und Versorgung.

Referenzen

[1] Deutscher Ethikrat (Hrsg.) (2012): Personalisierte Medizin – der Patient als Nutznießer oder Opfer? https://www.ethikrat.org/fileadmin/Publikationen/Dokumentationen/tagungsdokumentation-personalisierte-medizin.pdf (letzter Zugriff am 29.10.2018).

[2] European Science Foundation (Hrsg.) (2012): Personalised Medicine for the European Citizen – Towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM). http://archives.esf.org/fileadmin/Public_documents/Publications/Personalised_Medicine.pdf (letzter Zugriff am 15.10.2018).

[3] Statista (2018): Umsatz auf dem Markt für personalisierte Medizin nach Segmenten weltweit in den Jahren 2012 bis 2022 (in Milliarden US-Dollar). https://de.statista.com/statistik/daten/studie/686899/umfrage/umsatz-auf-dem-markt-fuer-personalisierte-medizin-nach-segmenten-weltweit (letzter Zugriff am 30.10.2018).

[4] Deutscher Ethikrat (2013): Die Zukunft der genetischen Diagnostik von der Forschung in die Anwendung. Stellungnahme. https://www.ethikrat.org/fileadmin/Publikationen/Stellungnahmen/deutsch/stellungnahme-zukunft-der-genetischen-diagnostik.pdf (letzter Zugriff am 29.09.2018).

[5] Hüsing B, Harting J, Bürlen B (2008): Individualisierte Medizin und Gesundheitssystem – Zukunftsreport. https://www.tab-beim-bundestag.de/de/pdf/publikationen/berichte/TAB-Arbeitsbericht-ab126.pdf (letzter Zugriff am 30.10.2018).

[6]: Dalton WS und Friend SH (2006): Cancer Biomarkers – An Invitation to the Table. Science; 312(5777): 1165–1168.

[7] Bookmann (2011): Gene-Environment Interplay in Common Complex Diseases: Forging an Integrative Model—Recommendations From an NIH Workshop. Genetic Epidemiology; 35(4): 217–225.

[8] Choi JR, Park SY, Noh OK et al. (2016): Gene mutation discovery research of non-smoking lung cancer patients due to indoor radon exposure. Annals of Occupational and Environmental Medicine; 28: 13.

[9] Pérez-Riera AR, Barbosa-Barros R, Daminello Raimundo R et al. (2018): The congential long QT syndrome Type 3: An update. Indian Pacing Electrophysiology Journal; 18(1): 25–35.

[10] Baniasadi S, Shokouhi SB, Tabarsi P et al. (2016): Prevalence of HLA-B*5701 and Its Relationship with Abacavir Hypersensitivity Reaction in Iranian HIV-Infected Patients**.** Tanaffos; 15(1): 48–52.

[11] Wen N, Wang Y, Wen L et al. (2014): Overexpression of FOXM1 predicts poor prognosis and promotes cancer cell proliferation, migration and invasion in epithelial ovarian cancer. Journal of Translational Medicine; 12:134.

[12] Aneesh TP, Sonal SM, Asha J et al. (2009): Pharmacogenomics: The Right Drug to the Right Person. Journal of Clinical Medicine Research; 1(4): 191-194.

[13] McLeod HL und Evans EW (2001): Pharmacogenomics: Unlocking the Human genome for better Drug Therapy. Annual Review of Pharmacology and Toxicology; 41:101–21.

[14] Verband der forschenden Pharmaunternehmen (VfA) (Hrsg.) (2018): vfa-Positionspapier „Personalisierte Medizin". https://www.vfa.de/embed/positionspapier-personalisierte-medizin.pdf (letzter Zugriff am 01.09.2018).

[15] Visscher PM, Wray NR, Zhang Q et al. (2017): 10 Years of GWAS Discovery: Biology, Function, and Translation. The American Journal of Human Genetics; 101:5–22.

[16] Stranger BE, Stahl EA, Raj T (2011): Progress and Promise of Genome-Wide Association Studies for Human Comlex Trait Genetics. Genetics; 187(2): 367–383.

[17] Trinidad SB, Fullerton SM, Bares JM et al. (2010): Genomic Research and Wide Data Sharing: Views of Prospective Participants. Genetics in Medicine; 12(8): 486–495.

[18] Middleton A (2018): Society and personal genome data. Human Molecular Genetics; 27(R1): R8–R13.

[19] Vermeulen E, Hennemann L, van El C et al. (2014): Public attitudes towards preventive genomics and personal interest in genetic testing to prevent disease: a survey study. European Journal of Public Health; 24(5):768-775.

[20] Venter JC, Adams MD, Myers EW et al. (2001): The Sequence of the Human Genome. Science; 291(5507):1304-51.

[21] National Human Genome Research Institute (2016): The Cost of Sequencing a Human Genome. https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome (letzter Zugriff am 01.09.2018).

[22] Beck TF, Mullikin JC, Biesecker LG (2016): Systematic Evaluation of Sanger Validation of Next-Generation Sequencing Variants. Clinical Chemistry; 62(4):7647–7654.

[23] Ke R, Mignardi M, Hauling T et al. (2016): Fourth Generation of Next-Generation Sequencing Technologies: Promise and Consequences. Human Mutation; 37(12):1363-1367

[24] Wetterstrand KA. (2018): DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP). https://www.genome.gov/sequencingcostsdata (letzter Zugriff am 30.10.2018).

[25] Beale S, Sanderson D, Sanniti A et al. A scoping study to explore the cost-effectiveness of next-generation sequencing compared with traditional genetic testing for the diagnosis of learning disabilities in children. Health Technology Assessment; 19(46):1-90.

[26] Xue Y, Ankala A, Wilcox W (2015): Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of nextgeneration sequencing: Single-gene, gene panel, or exome/genome sequencing. Genetics in Medicine; 17(6):444-51.

[27] Statistisches Bundesamt (Destatis) (2018): Gestorbene nach ausgewählten Todesursachen, Anzahl der Gestorbenen 2015. https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Gesundheit/Todesursachen/Tabellen/EckdatenTU.html;jsessionid=65CD5F116E2304175B9F15637FCC03F1.InternetLive1 (letzter Zugriff am 30.10.2018).

[28] Statistisches Bundesamt (Destatis) (2018): Krankheitskosten: Deutschland, Jahre, Krankheitsdiagnosen (ICD-10). https://www-
gene-
sis.destatis.de/genesis/online/data;sid=F15A87E6FF1B6BFB2C3FBCD90BBD00C4.GO_1_4?operation=abruftabelleBearbeiten&levelindex=2&levelid=1541076398917&auswahloperation=abruftabelleAuspraegungAuswaeh-
len&auswahlverzeichnis=ordnungsstruktur&auswahlziel=werteabruf&selectionname=23631-0001&auswahltext=&werteabruf=Werteabruf (letzter Zugriff am 01.11.2018).

[29] Chiou CF, Hay JW, Wallace JF et al (2003): Development and Validation of Grading System for Quality of Cost-Effectiveness Studies. Medical Care; 41(1):32–44.

[30] Carrasco-Ramiro F, Peiró-Pastor R, Aguado B (2017): Human genomics projects and precision medicine. Gene Therapy; 24(9):551-561.

[31] Lanscar E und Louviere J (2008): Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics; 26(8): 661-677.

[32] Schmidtke J und Rüping U (2013): Genetische Beratung: Nichtärztliche Personen können ein Gewinn sein. Deutsches Ärzteblatt; 110(25): A-1248 / B-1090 / C-1082.

Module der kumulativen Dissertation

Modul 1:

Plöthner M, Frank M, Graf von der Schulenburg JM: Cost analysis of whole genome sequencing in German clinical practice. The European Journal of Health Economics 2017; 18(5):623-633.

Modul 2:

Plöthner M, Frank M, Graf von der Schulenburg JM: Ganzgenomsequenzierung in der deutschen Versorgung: Ökonomische Auswirkungen eines Einsatzes in ausgewählten Anwendungsgebieten. Bundesgesundheitsblatt 2017; 60: 143-150.

Modul 3:

Kreis K, **Plöthner M,** Schmidt, T, Seufert R, Schreeb K, Jahndel V, Maas S, Kuhlmann A, Zeidler J, Schramm A: Healthcare costs associated with breast cancer in Germany – a claims data analysis. Eingereicht bei: The European Journal of Health Economics 2019.

Modul 4:

Plöthner M, Zeidler J, Graf von der Schulenburg JM: Individualisierte Medizin bei ausgewählten Krebserkrankungen. Public Health Forum 2016; 24(2): 131-134.

Modul 5:

Plöthner M, Ribbentrop D, Hartman JP, Frank, M: Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies: A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany. Advances in Therapy 2016; 33(9): 1461–1480.

Modul 6:

Tanner K, Kirchhof P, Graf von der Schulenburg JM, Wolfrum R, Gantner G, Molnár-Gábor F, Frank M **Plöthner M**: Genomanalysen als Informationseingriff: Ethische, juristische und ökonomische Analysen zum prädiktiven Potential der Genomsequenzierung, Schriften des Marsilius-Kollegs 2016. Band 15; Universitätsverlag Winter Heidelberg; 51-54; 71-75; 98-160; 168-171; 222-228.

Modul 7:

Plöthner M, Schmidt K, Schips C, Damm K: Which attributes of whole genome sequencing tests are most important to the general population? Results from a German preference study. Pharmacogenomics and Personalized Medicine 2018; 11: 7-21.

Modul 8:

Plöthner M, Meisgeier A, Kreis K, Graf von der Schulenburg JM: Humangenetische Beratungen im Rahmen prädiktiver genetischer Diagnostik – Eine Analyse der verfügbaren Kapazitäten im deutschen Setting.

Modul 9:

Plöthner M, Klora M, Rudolph D, Graf von der Schulenburg JM: Health-Related Genetic Direct-to-Consumer-Tests in the German Setting: The Available Offer and the Potential Implications for a Solidary Financed Health-Care System. Public Health Genomics 2017; 20(4):203-217. Verlag: S. Karger AG.

Modul 1

Cost analysis of whole genome sequencing in German clinical practice

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Cost Analysis of Whole Genome Sequencing in German Clinical Practice

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Abstract

Objectives: Whole genome sequencing (WGS) is an emerging tool in clinical diagnostics. However, little has been said about its procedure costs, owing to a dearth of related cost studies. This study helps fill this research gap by analysing the execution costs of WGS within the setting of German clinical practice.

Methodology: First, to estimate costs, a sequencing process related to clinical practice was undertaken. Once relevant resources were identified, a quantification and monetary evaluation was conducted using data and information from expert interviews with clinical geneticists, and personnel at private enterprises and hospitals. This study focuses on identifying the costs associated with the standard sequencing process, and the procedure costs for a single WGS were analysed on the basis of two sequencing platforms—namely, HiSeq 2500 and HiSeq Xten, both by Illumina, Inc. In addition, sensitivity analyses were performed to assess the influence of various uses of sequencing platforms and various coverage values on a fixed-cost degression.

Results: In the base case scenario—which features 80% utilization and 30-times coverage—the cost of a single WGS analysis with the HiSeq 2500 was estimated at €3,858.06. The cost of sequencing materials was estimated at €2,848.08; related personnel costs of €396.94 and acquisition/maintenance costs (€607.39) were also found. In comparison, the cost of sequencing that uses the latest technology (i.e. HiSeq Xten) was approximately 63% cheaper, at €1,411.20.

Conclusion: The estimated costs of WGS currently exceed the prediction of a 'US$1000 per genome', by more than a factor of 3.8. In particular, the material costs in themselves exceed this predicted cost.

Keywords: Whole genome sequencing; Cost analysis; German clinical practice

Introduction

Whole genome sequencing (WGS) is an emerging diagnostic tool, and it has the potential to generate an incomparable variety of genetic information. Individual genomes and genetic variations within the population can be characterized by genetic analyses [1]. In recent years, a better understanding of the relationship between genotype and phenotype has been achieved by conducting genome-wide association studies [2]. Hence, this genetic research, in concert with current technological progress, has provided the prerequisites for a broad application of genetic diagnostics (e.g. WGS) in medical care.

On account of continuous technological progress, significant cost reductions with respect to DNA sequencing have been realized over time [3]. This cost degression has been facilitated by the transition from the classic chain termination method ('Sanger method' [4]) to next-generation sequencing (NGS) technologies [1, 5]. The massively parallel sequencing inherent in NGS allows for high-throughput sequencing at low costs [6]. A range of various NGS technologies currently exist, from a number of different companies [7] (e.g. HiSeq, from Illumina; 454, from Roche Applied Science; Solid, from Applied Biosystems). These platforms are characterized by different approaches and can differ in terms of several technical specifications, such as sequencing cost per gigabyte (Gb), run time, reported accuracy, read length, observed raw error rate, sequence yield per run, insert size, instrument cost, and DNA requirements [8].

With this evolution in sequencing technologies, there has been ongoing progress in the field of genomics [9]. Hence, there has been an exponential increase in the use of various WGS applications in research and clinical practice [5], and it is expected to become a standard diagnostic tool in clinical practice [10, 11]. WGS has two general diagnostic potentials—namely, as a diagnostic instrument for manifested diseases [12] and as a predictive tool for determining disease dispositions [13, 14]. In many cases, WGS's diagnostic and predictive potentials enhance patient benefits. In oncology, for example, a better understanding of cancer genetics, in tandem with improved disease diagnosis, prognosis, and management, can be achieved through the use of WGS. In the field of rare diseases, or in patients with an abnormal or an unknown phenotype, WGS may provide a diagnosis [15] and has the potential to end a diagnostic odyssey [16]. With a predictive approach, WGS may identify genetic variations, and predispositions to an increased risk for specific diseases [17]; for example, BRCA I and BRCA II are genetic mutations commonly linked to breast cancer [18]. Knowledge of various predispositions—as well as of incidental findings that are independent of previous diagnostic issues [19, 20]—can affect patient health through screening; it can also help mitigate risk and act as a part of various prevention measures [21]. Indeed, the results of WGS analyses can have far-reaching implications for patients [22]. The acquisition of genetic information can not only lead to behavioural changes in patients and their

family members [23], but also increase the use of further diagnostics and of preventive and therapeutic procedures.

However, until recently, the diagnostic application of WGS was unthinkable, given its high procedure costs [24]. The cost of first decoding a human genome amounted to approximately US$3 billion [25]; even as of 2001, the cost of WGS was estimated at about US$100 million [26]. Meanwhile, technology firms yield at performing a WGS for less than US$1,000 per genome [27–29]. However, the literature lacks relevant cost studies [30]. Additionally, it is necessary to consider and evaluate costs related to the clinical implementation of, and reimbursements for, undertaking WGS. Thus, in consideration of scarce resources and increasing expenses in the area of German healthcare, cost analyses in the run-up to WGS implementation as a diagnostic method are of significance. With this in mind, we conducted analyses of the costs of executing WGS, particularly in the context of German clinical practice.

Methodology

The creation of a standardized quality-assured process for WGS analysis, on the basis of procedures in the German Cancer Research Center (DKFZ), Heidelberg, constituted a starting point for the analysis described herein. The various steps within this process are defined with the help of expert opinions and clinical routines; thereafter, resources used in support of the process are identified. The overall costs per genome mainly depend on the applied sequencing platform used; hence, two sequencing platforms by DKFZ's sequencing technology provider (i.e. Illumina, Inc.) were chosen. The first of these is the HiSeq 2500 (Illumina Inc.; San Diego, CA, USA), which is currently the standard device for high-throughput sequencing in most clinical facilities; the second—namely, the HiSeq Xten (Illumina Inc.; San Diego, CA, USA)—is the latest development in high-throughput sequencing, and it was studied to compare the effects of higher throughput.

General methodology

Step 1: Resource identification

Drawing on standard DKFZ processes, a quality-assured WGS process was generated. For this cost calculation, an institutional perspective was selected; indirect personnel costs were not calculated. Generally, single costs can be directly allocated to WGS, whereas while overhead costs are essential to the examination and organization of a WGS, they cannot be initially assigned to a single sequencing process. Hence, only direct medical costs and site-specific costs for sequencing devices essential to WGS execution were included; all other site-specific nonmedical direct costs and overhead costs (e.g. water, energy, administration expenses, and the use of IT infrastructure) were excluded from the analysis. Moreover, personnel costs were categorized as those pertaining to medical, technical, and bioinformatics personnel.

Step 2: Resource quantification

In the second step, the identified resources were quantified. It should be noted that complete utilization (i.e. 100%) of the sequencing platforms is implausible, owing to maintenance, failures, cleaning, and missing sequencing assignments. Therefore, the effects of different utilization levels were analysed, via sensitivity analysis. In this step, the influence of other levels of utilization (i.e. 90%, 80%, 70%, and 60%) on costs was simulated. Taking into account economies of scale and fixed-cost degression, the average costs of WGS were found to decrease with higher levels of utilization. Moreover, the depth of sequencing (coverage) is a substantial cost-influencing factor and correlates with error rate, amount of data generated, as well as the amount of genomes per run. In line with the desired level of accuracy, the coverage rate was chosen, and this rate influenced the amount of genomes per run; therefore, sensitivity analysis was undertaken with regards to various coverage values (i.e., 10×, 15×, 30×, 60×, and 75×). An increase in the average costs was found with increased coverage and the accompanying reduction in the number of genomes per run.

Step 3: Resource evaluation

In this step, the identified and quantified resources were assessed in terms of monetary value. These monetary valuations were based on data and information provided by human genetic experts, hospitals, and private cooperation partners. Data used in the sequencing equipment and other materials were provided by Illumina, Inc., and their costs are based on the company's list prices. The personnel working time for a single task was estimated, using data from expert interviews. Subsequently, time estimations were valuated through the use of monetary mean values. Personnel costs for chemical–technical assistants (CTA) and bioinformaticians were calculated on the basis of the German civil service collective agreement of the federal state (TV-L) of Baden–Württemberg. Different pay-scale levels were used in these calculations: for bioinformaticians, a weekly working time of 39 hours and an annual gross salary of €55,902.84 (€0.50 per minute) were assumed, and for CTAs, a weekly working time of 39 hours and an annual gross salary of €40,809.33 (€0.36 per minute) were assumed. The payroll expenses for specialized clinical geneticists were based on the civil service collective agreement for physicians at the university clinics of the federal state of Baden–Württemberg; hence, a weekly working time of 39.30 hours and an annual gross salary of €87,543.96 (€0.77 per minute) were assumed. For obtaining a blood sample, costs of €5.65—according to the uniform value scale, the basis of pricing of ambulant services (EBM)—were assumed. For an adequate calculation of the annual costs of acquisition and maintenance, we used the annuity method [31]. In this way, annual payments consisting of interest and redemption were calculated. For this purpose, an interest rate of 3% was assumed.

Base case scenario

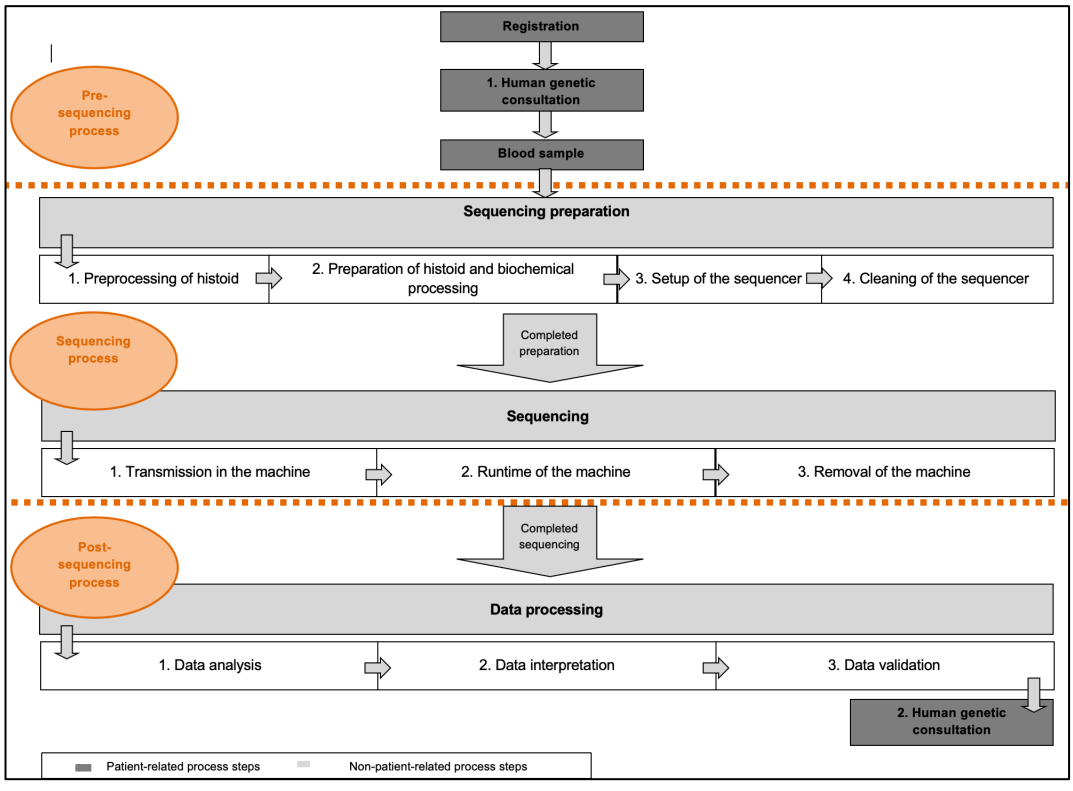
The cost of a single WGS analysis is influenced by several aspects, including the examination aim, clinical setting, technical aspects, data generation, and the use of sequencing platforms. In addition, depending on the aim of the examination, divergences emerge in diagnostic settings (in-patient vs. out-patient), scope of genetic counselling (general genetic screening vs. specific clinical issue), and genetic material acquisition (operation vs. blood test). For this reason, we defined a base case scenario. WGSs are typically performed when a rare disease is suspected. An out-patient setting in which genetic material is obtained via a blood sample is assumed. The clarification of secondary findings (e.g. according to the gene list of the American College of Medical Genetics and Genomics (ACMG)) was not included. Furthermore, the base case scenario is hallmarked by certain technical aspects, such as a sequencing platform utilization setting of 80% and 30-times coverage.

Results

Process structure

The cost analysis was based on the identification of relevant process steps. The process chart is illustrated in Fig. 1.

Fig. 1 WGS analysis process chart



A three-step process structure was created that comprised pre-sequencing (direct patient contact and administration), sequencing (mechanical and biochemical processing of genetic material), and post-sequencing process (evaluation and final clinical genetic consultation).

Step 1: Identification of necessary resources

The pre-sequencing process is characterized by direct patient contact. The first step prior to the diagnostic examination is patient administration. The pre- and post-sequencing clinical genetic consultation is, unlike research, an indispensable component of patient-centred quality management in clinical genetic care. The informed consent process, regarding opportunities and risks as well as the arrangement of relaying findings, is an important part of clinical genetic consultation. The time required for these medical consultations depends on the aim of the medical examination and the consequences of the patient results. In addition, genetic material is generally extracted from blood samples, smear tests, or during surgical interventions, and so they incur costs at a variety of levels. The included costs of the pre-sequencing process comprise the personnel costs for the clinical geneticist and administrative employees, as well as the costs related to a blood sample.

During the sequencing process, the costs of diagnostic examinations emerge. The essential work steps are the mechanical and biochemical processing of genetic material, followed by the setting up of sequencing devices and cleaning. Additional costs in the sequencing process include personnel cost for technical staff, sequencing material and allocated costs for the acquisition and maintenance of sequencing platforms.

The post-sequencing process is divided into the analysis, interpretation, and validation of acquired data, and final clinical genetic consultation, which includes conveying the findings to patients. In this step, the included personnel costs are those associated with clinical geneticists and bioinformaticians.

Steps 2 and 3: Quantification and monetary valuation of resources

Costs of the pre-sequencing process

The pre-sequencing process is mainly characterized by personnel costs for initial clinical genetic consultation. With a time exposure of 45–60 minutes for this clinical genetic consultation, costs of €40.43 per WGS at an average time exposure of 52.5 minutes arise. Furthermore, costs of €5.65 for obtaining a blood sample were incurred; hence, the total cost for the pre-sequencing process amounts to €46.08.

Costs of sequencing process

The sequencing process costs consist of those for personnel such as technical staff and sequencing material, as well as costs allocated to the acquisition and maintenance of sequencing platforms.

Personnel costs

CTA personnel costs scarcely differ between the HiSeq 2500 and HiSeq Xten (Table 1). Moreover, it was found that the preparation of histoid is the most time-consuming step in the sequencing process, and it incurs personnel costs of €108.00.

Table 1 Personnel costs for CTA in sequencing process and time exposure per genome

Work step	**Average exposure time (in minutes)**		**Mean wage per WGS (in €)**	
	HiSeq 2500	HiSeq Xten	HiSeq 2500	HiSeq Xten
DNA extraction	15	15	5.40	5.40
Reprocess histoid (amplification on cBot[a])	37.5	-	13.50	-[b]
Prepare histoid and biochemical processing	300	300	108.00	108.00
Setup sequencer[c]	2	1.25	0.72	0.45
Clean sequencer[d]	3.5	2.19	1.26	0.79
Handover of histoid in the machine	10	10	3.60	3.60
Removal of histoid from the machine	10	10	3.60	3.60
Total			**136.08**	**121.84**

[a] A cBot is an automatic system that generates from DNA (single molecule) matrix clones and prepares these for sequencing through synthesis [32]

[b] The HiSeq Xten is an onboard clustering system that does not require a cBot. Hence, these costs were not included in the sequencing personnel cost of the HiSeq Xten

[c] The costs of this work step vary according to flowcell utilization. An average time exposure of 20 minutes was stated per run. Hence, with 30-times coverage, the time exposure was distributed to ten genomes on the HiSeq 2500 and to 16 genomes on the HiSeq Xten

[d] The costs of this work step vary according to flowcell utilization. An average time exposure of 35 minutes was stated per run for one machine. Hence, with 30-times coverage, the time exposure is distributed to ten genomes on the HiSeq 2500 and to 16 genomes on the HiSeq Xten

Acquisition costs and maintenance costs

The acquisition costs of the sequencing platform on a per-genome basis amount to €485.29 for the HiSeq 2500, and €199.89 for the HiSeq Xten (Table 2). Despite the distinct lower acquisition costs associated with the HiSeq 2500, its higher per-genome cost emerges as a result of the time and quantity of genomes per run. This shows that the 'time per run' and the 'number of sequenced genomes per run' significantly influences overall costs. The operating life (which is synonymous with the technology life) is three years; given 80% utilization, 30-times coverage, and a machine lifetime of three years, a maximum of 1,458 human genomes can be sequenced with the HiSeq 2500, and 46,716 human genomes with the HiSeq Xten.

In addition, fixed costs for technical service and maintenance were found to be significant. Allocated costs for maintenance and service agreements amount to €122.11 for HiSeq 2500 and € 41.38 for HiSeq Xten per genome (Table 2).

Table 2 Acquisition and maintenance costs per genome

Basic machine characteristics	**HiSeq 2500**	**HiSeq Xten**
Genomes per run	10	160[a]
Days per run	6	3
Quantity of genomes in one year at a utilization rate of 80%	486	15,564
Acquisition cost for platform and cBot (in €)		
Total acquisition costs	667,128.00	8,800,000.00
Apportionment to three years of operating life[b]	235,850.00	3,111,067.20
Acquisition costs per genome	**485.29**	**199.89**
Maintenance costs (in €)		
Machine	78,313.00	910,800.00
cBot	5,620.00	-
Total maintenance costs[c]	167,866.00	1,821,600.00
Apportionment to three years of operating life[d]	59,345.73	643,990.91
Maintenance costs per genome	**122.11**	**41.38**

[a] One HiSeq Xten consists of 10 HiSeq 2500 machines; we calculate the acquisition costs per machine. On one HiSeq 2500 on the HiSeq Xten platform, 16 genomes per run can be sequenced; hence, 160 genomes are the maximum quantity of genomes per run on a HiSeq Xten

[b] The three-year operating time (for platform and cBot) was furnished by the manufacturer. For the apportionment to three years, the annuity method with an interest rate of 3% was used

[c] Maintenance costs do not accrue during the first year; however, to achieve a uniform distribution, two years of maintenance costs were apportioned over three years

[d] For the apportionment to three years, the annuity method with an interest rate of 3% was used

Material costs

The costs associated with sequencing materials represent an essential cost factor, and they are split into 16 (per machine) and ten human genomes per run for the HiSeq Xten and HiSeq 2500, respectively. However, it should be noted that 160 genomes can be sequenced simultaneously on the HiSeq Xten. The material costs per run for sequencing with the HiSeq Xten are significantly higher than those with the HiSeq 2500. Nevertheless, dividing the material costs across a large number of analyses leads to significantly lower costs per genome for the HiSeq Xten (Table 3).

Table 3 Sequencing material costs per whole genome

Costs for sequencing material (in €)	HiSeq 2500	HiSeq Xten[a]
Number of genomes per run	10	16
Fixed costs per run		
Two flowcells[b]	10,754.00[c]	4,569.00[d]
Sequencing chemistry	17,426.00[e]	7,455.00[f]
Variable costs per run[g]		
Template preparation[h]	274.60	439.36
DNA extraction[i]	26.20	41.92
Run total	28,480.80	12,505.28
Material costs per run	**2,848.08**	**781.58**

[a] Consists of 10 HiSeq 2500 machines.
[b] Flowcell indicates the Illumina flowcell, which is a planar optically transparent surface similar to a microscope slide that contains a lawn of oligonucleotide anchors bound to its surface [33].
[c] Costs arise from using the product TruSeq SBS Kit v3 – HS (200 cycles).
[d] Costs arise from using the product HiSeqX Ten Reagent Kit v2. However it should be noted that the flowcells and chemicals are available in a complete kit.
[e] Costs arise from using the TruSeq PE Cluster kit v3 – cBot – HS.
[f] Costs arise from using the HiSeqX Ten Reagent Kit v2.
[g] These costs are not subject to the fixed-cost degression.
[h] For template preparation, a TruSeq DNA Nano Sample Preparation Kit and a TruSeq DNA PCR-free Sample Preparation kit can be used. Costs of €27.46 per sample/genome arise.
[i] Costs of €2.62 per genome arise from using a QIAamp DNA Blood Mini Kit [34].

Sensitivity analysis of workload and coverage differentiation

The results of the two sensitivity analyses are shown in the appendix (Tables 5, 6). On account of larger economies of scale and fixed-cost degression, the average costs of a WGS analysis are reduced in relation to output quantity (Table 5). Assuming 80% utilization, the total cost for materials, acquisition, and maintenance is €3,455.48 and €1022.85 per genome for the HiSeq 2500 and HiSeq Xten, respectively. On the other hand, the costs per genome increase with an increase in coverage rate: a doubling of the coverage rate leads to a halving of the quantity of genomes per flowcell. For example, an increase in coverage from 30 times to 60 times reduces the number of genomes per run, from 10 genomes to five on the HiSeq 2500. Hence, the costs associated with materials, acquisition, and maintenance increase to €6,880.88 (Table 6).

Post-sequencing process costs

Personnel costs comprise an important cost factor in the post-sequencing process. These costs can be categorized as those for clinical geneticists and those for bioinformaticians. The mean cost of clinical geneticists is €40.43 for the final clinical genetic consultation, for an average time exposure of 52.5 min. Additional costs stem from work associated with bioinformatical interpretation; the duration of this task depends on the specific issue at hand, and can range from one hour to a few days. However, in line with the base case scenario, six working hours was assumed. Hence, costs of €180.00 arise from undertaking a read-quality check (possible with read trimming), the identification of single nucleotide polymorphisms (SNP) or mutations, and the interpretation of identified SNPs or mutations.

Overall costs

Currently, the cost of a WGS analysis in a clinical setting in Germany is €3,858.06 assuming 80% utilization of the sequencing platform and a 30-times coverage with a HiSeq 2500. By using the latest high-throughput technology (i.e. HiSeq Xten), the overall cost could be reduced by 63%, to €1,411.20. The sequencing process—especially the sequencing materials and allocated investment costs—was identified as the most expensive WGS component. The results are summarized in Table 4.

Table 4 Overall costs of WGS analysis with 80% utilization (characterized by an annual throughput of 486 genomes on a HiSeq 2500 and 15,564 genomes on a HiSeq Xten)

Cost per process step (in €)	HiSeq 2500	HiSeq Xten
Pre-sequencing process		
Obtaining blood sample	5.65	5.65
Personnel costs		
Clinical geneticist	40.43	40.43
Total pre-sequencing process	46.08	46.08
Sequencing process		
Personnel costs		
CTA	136.08	121.84
Costs of specific departments		
Allocated acquisition costs	485.29	199.89
Allocated maintenance costs	122.11	41.38
Sequencing materials	2,848.08	781.58
Total sequencing process	3,591.56	1,144.69
Post-sequencing process		
Personnel costs		
Human genetics	40.43	40.43
Bioinformatics	180.00	180.00
Total post-sequencing process	220.43	220.43
Total (in €)	**3,858.06**	**1,411.20**

Discussion

Currently, the cost of a WGS analysis in a clinical setting in Germany is €3,858.06. To determine the costs of implementing this diagnostic procedure, evidence related to associated expenses is needed. In addition to medical evidence, cost evaluations are important to medical decision-makers; more importantly, especially for WGS, it is essential to determine which procedures will have a potentially high economic impact, and so reliable cost evaluations are necessary.

The overall costs of a WGS analysis depends on a plurality of aspects; in the following, the main cost-influencing factors—such as the sequencing platform used, the material costs, and the coverage rate—are highlighted. The selection of a high-throughput technology is the first major strategic decision in WGS implementation; this selection affects investment and maintenance

expenses, as well as costs related to the sequencing materials that will be used. The results of this analysis showed that with a utilization rate of 80% of the sequencing platform, the allocated acquisition costs of HiSeq Xten were about 60% lower than those of HiSeq 2500, owing to higher throughput; the situation is similar for the costs of sequencing materials, which comprise the main cost factor in executing WGS analyses. Costs per genome are substantially influenced by the utilization of sequencing platforms and flowcells, as a result of the fixed-cost degression; hence, adopting the latest technology seems to be a precondition to keeping the average cost low. However, these circumstances need to be considered with caution. Keeping the average cost low assumes that a specific demand for genetic analysis, as well as a certain rate of utilization, is achieved. One HiSeq Xten has a significantly higher capacity (i.e. one HiSeq Xten can replace 32 HiSeq 2500 machines), and implementation may lead to significant overcapacity. Therefore, calculations that assume a utilization rate of 80% for the HiSeq Xten might be overly high, and may therefore provide too-optimistic cost calculations. Lower utilization leads to an apportionment of fixed costs to fewer genomes, and thus to higher costs per genome. Hence, before a new sequencing platform is implemented, calculations of the probable number or future needs of WGS analysis during the operating time should be conducted. Moreover, future directions of the demand for WGS can scarcely be assessed at this time; this demand depends, for example, on national reimbursement regulations. The establishment of a limited number of WGS execution sites, perhaps in the form of centres, could possibly lead to the cost-effective execution of WGS; effective management and better utilization of sequencing platforms may help achieve these lower costs. However, genetic analyses are an emerging tool, and demand for its use will gradually increase. Therefore, technology firms should also look to develop platforms (e.g. HiSeq 4000 by Illumina, Inc.) with a higher utilization rate (relative to the HiSeq 2500) and lower acquisition costs (relative to the HiSeq Xten) to deal with what will no doubt be increasing demand, and to address the potential for significant overcapacity.

Test quality and costs correlate with the selection of coverage rate, which in turn influences the sensitivity of detection [35]. The selection of coverage rate is based on the intended validity of genetic analysis results. At this point, 30-times coverage is the customary benchmark for high-quality genome data [36]. However, with complex heterogenic genetic structures, the sequencing of tumours (for example) is largely conducted with significantly higher coverage rates [37, 38]. In general, the selection of coverage influences not only the number of genomes per run—and thus the costs per genome—but also (depending on the various amounts of genetic data) the cost of data storage and evaluation.

The highest personnel costs arise from bioinformatical work steps. The interpretation process is influenced by the purpose behind the examination, as well as the experience of the

bioinformatician involved. (These factors result in a wide range of time estimations, from 1 hour to a few days.) The time needed for data interpretation also depends on clinical issues, dataset size, and the hardware IT infrastructure being used. Costs associated with data validation—an additional cost-influencing work step—are difficult to calculate. Validations were conducted only if disease-relevant mutations are identified; these mutations and biomarkers were verified using traditional Sanger technology, which is the current 'gold standard' [39]. Conspicuous genetic features differ in frequency and by patient; however, an estimation of the frequency of specific conspicuous genetic features was not available. Hence, validation costs cannot be depicted.

Due to site specificity, cost-increasing factors—such as overhead and the costs of IT infrastructure and data storage—were excluded from the cost analysis. IT costs constitute a substantial part of investment costs, and long-term cooperation, quantity effects, and discounts determine these site-specific costs; they can also create substantial differences between list and project prices. Moreover, overhead—such as energy, water, rent, and administration costs—are characterized by high variability. Nevertheless, these costs should be considered in WGS reimbursement decisions.

Other limitations of this study include the single evaluation of WGS processes in DKFZ, the constraint of using a single technology, the fact that monetary evaluations are estimations made by clinical genetic experts, and the fact that data are from a single technology provider. The process chart is influenced by the specific structural organization of and processes in the DKFZ, and may differ with each institution or hospital. Investment, maintenance, and material costs were provided by Illumina, Inc.; these data were most appropriate in ensuring the study's high representativeness, owing to the largest market share of the NGS market and therefore the worldwide distribution of sequencing platforms [40, 41]. It is noteworthy that the use of a sequencing platform from another provider may lead to different cost estimates.

An important finding of this study is that cost analyses for WGS, as an innovative diagnostic tool, cannot be generalized. Variations in relevant cost-influencing factors will necessarily lead to different overall costs. Therefore, the following aspects should be considered in any cost assessment of WGS: (1) the use of an inpatient versus outpatient setting, (2) the diagnostic context at hand (e.g. the costs of using WGS to inform cancer care differ greatly from those of using WGS to diagnose a rare disease, especially within the scope of genetic counselling), (3) the approach and technology used (e.g. different costs per Gb and time for sequencing), (4) the cost factors to be included (no consensus exists as to which cost factors should be included in a cost analysis of WGS), (5) the experience of the personnel involved (experience may influence processing time, including bioinformatical interpretations), and (6) regulations informed by secondary or incidental findings (e.g. confirmation with Sanger technology).

This study shows that, to date, the US$1,000 genome has not become a reality in German quality-assured health care settings. However, technological progress may lead to further cost reductions, and so it may be possible to eventually achieve an even lower price for a single WGS [42]. The sole consideration in the development of costs for materials, acquisition, and maintenance—or the cost per Megabase of DNA Sequence [26]—suggests that, in the relatively near future, a US$1,000 genome may become a reality. However, other process-relevant factors that ensure a quality WGS execution are both integral parts and fixed components of this process, and they are not subject to such cost reductions over time.

In addition to improvements to sequencing platforms, both databases and bioinformatics tools may be improved in the near future. Databases are prerequisite to genome-wide association studies. Databases are growing in size, and the body of knowledge on phenotype–genotype correlations will also steadily increase in size. Besides the increased body of genetic knowledge, improvements in bioinformatics tools will facilitate both faster and cheaper assessments of the pathogenicity of (novel) variants; in this way, faster and more precise diagnoses will be possible. These conditions offer considerable benefits in terms of patient care. Improvements in diagnosis, especially of diseases of an unknown phenotype, can also affect the cost-effectiveness of WGS; besides possible cost reductions, improvements in patient care (e.g. quality of life, time of diagnosis, and diagnosis and treatment options) may also lead to increased cost-effectiveness.

However, there are numerous ethical, legal, and economic barriers inherent in the unrestricted use of WGS. Given the predictive potential of using WGS, an increase in costs on account of incidental use is feared. Incidental findings may lead to further diagnostics, as well as preventive and therapeutic procedures. The development of these consequential follow-up costs—many of which are caused by behavioural changes in patients, physicians, and family members—cannot be assessed with certainty today. Hence, the widespread application of WGS should be rejected, and its use should be indicated only under certain conditions [15]. The unrestricted application of WGS, in tandem with a lack of limitations on feedback practices, will lead to an unquantifiable increase in healthcare expenses. Limitations on specific indications can prevent increases in expenditures. Therefore, defining the criteria by which WGS is indicated is a future responsibility for policy decision-makers. Furthermore, data security, the effects of genetic information on insurance policies and employment agreements, and the extent of insurance benefits are critical issues that relate to the application of WGS. In addition, certain regulations should be adopted prior to implementation [43–45].

Conclusion

The calculated cost of a single WGS was estimated at €3,858.06 while assuming 80% capacity utilization with the sequencing platform widely used in Germany. Although this study focused on medical costs, to derive a comprehensive illustration of costing in a quality-assured healthcare system, overhead should also be considered. Moreover, because of the high costs associated with a single WGS analysis, the application of this analysis should be limited to specific indications that promise substantial medical benefits for patients. Technical progress may lead to a further reduction in the cost of WGS analysis, and so the application of WGS in medical care as a diagnostic, predictive, and prognostic tool is most likely to become more widespread in future medical care.

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References

1. Bentley, D.R et. al.: Accurate whole human genome sequencing using reversible terminator chemistry. Nature **456**(7218), 53–59 (2008). doi: 10.1038/nature07517
2. Rockman, M.V.: Reverse engineering the genotype-phenotype map with natural genetic variation. Nature **456**(7223), 738–744 (2008). doi: 10.1038/nature07633
3. Shendure, J., Ji, H.: Next-generation DNA sequencing. Nature biotechnology **26**(10), 1135–1145 (2008). doi: 10.1038/nbt1486
4. Sanger, F., Nicklen, S., Coulson, A.R.: DNA sequencing with chain-terminating inhibitors. Proceedings of the National Academy of Sciences of the United States of America **74**(12), 5463–5467 (1977)
5. Renkema, K.Y., Stokman, M.F., Giles, R.H., Knoers, Nine V A M: Next-generation sequencing for research and diagnostics in kidney disease. Nature reviews. Nephrology **10**(8), 433–444 (2014). doi: 10.1038/nrneph.2014.95
6. Grada, A., Weinbrecht, K.: Next-generation sequencing: methodology and application. The Journal of investigative dermatology **133**(8), e11 (2013). doi: 10.1038/jid.2013.248
7. Buermans, H P J, den Dunnen, J T: Next generation sequencing technology: Advances and applications. Biochimica et biophysica acta **1842**(10), 1932–1941 (2014). doi: 10.1016/j.bbadis.2014.06.015
8. Quail, M.A., Smith, M., Coupland, P., Otto, T.D., Harris, S.R., Connor, T.R., Bertoni, A., Swerdlow, H.P., Gu, Y.: A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers. BMC genomics **13**, 341 (2012). doi: 10.1186/1471-2164-13-341
9. Liu, L., Li, Y., Li, S., Hu, N., He, Y., Pong, R., Lin, D., Lu, L., Law, M.: Comparison of next-generation sequencing systems. Journal of biomedicine & biotechnology **2012**, 251364 (2012). doi: 10.1155/2012/251364
10. Green, E.D., Guyer, M.S.: Charting a course for genomic medicine from base pairs to bedside. Nature **470**(7333), 204–213 (2011). doi: 10.1038/nature09764
11. Kingsmore, S.F., Saunders, C.J.: Deep sequencing of patient genomes for disease diagnosis: when will it become routine? Science translational medicine **3**(87), 87ps23 (2011). doi: 10.1126/scitranslmed.3002695
12. Choi, M., Scholl, U.I., Ji, W., Liu, T., Tikhonova, I.R., Zumbo, P., Nayir, A., Bakkaloğlu, A., Ozen, S., Sanjad, S., Nelson-Williams, C., Farhi, A., Mane, S., Lifton, R.P.: Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. Proceedings of the National Academy of Sciences of the United States of America **106**(45), 19096–19101 (2009). doi: 10.1073/pnas.0910672106
13. Carlson, C.S., Eberle, M.A., Kruglyak, L., Nickerson, D.A.: Mapping complex disease loci in whole-genome association studies. Nature **429**(6990), 446–452 (2004). doi: 10.1038/nature02623
14. Meuwissen, T., Goddard, M.: Accurate prediction of genetic values for complex traits by whole-genome resequencing. Genetics **185**(2), 623–631 (2010). doi: 10.1534/genetics.110.116590
15. ACMG Board of Directors: Points to consider in the clinical application of genomic sequencing. Genetics in medicine: official journal of the American College of Medical Genetics **14**(8), 759–761 (2012). doi: 10.1038/gim.2012.74
16. Sawyer, S.L., Hartley, T., Dyment, D.A., Beaulieu, C.L., Schwartzentruber, J., Smith, A., Bedford, H.M., Bernard, G., Bernier, F.P., Brais, B., Bulman, D.E., Warman Chardon, J., Chitayat, D., Deladoëy, J., Fernandez, B.A., Frosk, P., Geraghty, M.T., Gerull, B., Gibson, W., Gow, R.M., Graham, G.E., Green, J.S., Heon, E., Horvath, G., Innes, A.M., Jabado, N., Kim, R.H., Koenekoop, R.K., Khan, A., Lehmann, O.J., Mendoza-Londono, R., Michaud, J.L., Nikkel, S.M., Penney, L.S., Polychronakos, C., Richer, J., Rouleau, G.A., Samuels, M.E., Siu, V.M., Suchowersky, O., Tarnopolsky, M.A., Yoon, G., Zahir, F.R., Majewski, J., Boycott, K.M.: Utility of

whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. Clinical genetics (2015). doi: 10.1111/cge.12654
17. Berg, J.S., Khoury, M.J., Evans, J.P.: Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genetics in medicine: (6), 499–504 (2011). doi: 10.1097/GIM.0b013e318220aaba
18. Ford, D., Easton, D.F., Stratton, M., Narod, S., Goldgar, D., Devilee, P., Bishop, D.T., Weber, B., Lenoir, G., Chang-Claude, J., Sobol, H., Teare, M.D., Struewing, J., Arason, A., Scherneck, S., Peto, J., Rebbeck, T.R., Tonin, P., Neuhausen, S., Barkardottir, R., Eyfjord, J., Lynch, H., Ponder, B., Gayther, S.A., Birch, J.M., Lindblom, A., Stoppa-Lyonnet, D., Bignon, Y., Borg, A., Hamann, U., Haites, N., Scott, R.J., Maugard, C.M., Vasen, H., Seitz, S., Cannon-Albright, L.A., Schofield, A., Zelada-Hedman, M.: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The American Journal of Human Genetics **62**(3), 676–689 (1998). doi: 10.1086/301749
19. Green, R.C., Berg, J.S., Grody, W.W., Kalia, S.S., Korf, B.R., Martin, C.L., McGuire, A.L., Nussbaum, R.L., O'Daniel, J.M., Ormond, K.E., Rehm, H.L., Watson, M.S., Williams, M.S., Biesecker, L.G.: ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genetics in medicine: official journal of the American College of Medical Genetics **15**(7), 565–574 (2013). doi: 10.1038/gim.2013.73.
20. Knoppers, B.M., Deschênes, M., Zawati, M.H., Tassé, A.M.: Population studies: return of research results and incidental findings policy statement. European journal of human genetics: EJHG **21**(3), 245–247 (2013). doi: 10.1038/ejhg.2012.152
21. Evans, J.P., Skrzynia, C., Burke, W.: The complexities of predictive genetic testing. BMJ (Clinical research ed.) **322**(7293), 1052–1056 (2001)
22. Dondorp, W.J., de Wert, Guido M.W.R.: The 'thousand-dollar genome': an ethical exploration. European journal of human genetics: **21 Suppl 1**, S6-26 (2013). doi: 10.1038/ejhg.2013.73
23. McBride, C.M., Koehly, L.M., Sanderson, S.C., Kaphingst, K.A.: The behavioral response to personalized genetic information: will genetic risk profiles motivate individuals and families to choose more healthful behaviors? Annual review of public health **31**, 89–103 (2010). doi: 10.1146/annurev.publhealth.012809.103532
24. Ten Bosch, John R, Grody, W.W.: Keeping up with the next generation: massively parallel sequencing in clinical diagnostics. The Journal of molecular diagnostics : JMD **10**(6), 484–492 (2008). doi: 10.2353/jmoldx.2008.080027
25. National Human Genome Research Institute: The Human Genome Project Completion: Frequently Asked Questions (2010). https://www.genome.gov/11006943. Assessed 17 July 2015
26. Wetterstrand, K.A.: DNA sequencing costs: data from the NHGRI Genome Sequencing Program. http://www.genome.gov/sequencingcosts. Assessed 13 January 2015
27. Collins, F.: Has the revolution arrived? Nature **464**(7289), 674–675 (2010). doi: 10.1038/464674a
28. Hayden, E.C.: Technology: The $1,000 genome Nature (2014). Nature **507**(7492), 294–295 (2014). doi: 10.1038/507294a
29. Service, R.F.: Gene sequencing. The race for the $1000 genome. Science (New York, N.Y.) **311**(5767), 1544–1546 (2006). doi: 10.1126/science.311.5767.1544
30. Frank, M., Prenzler, A., Eils, R., Graf von der Schulenburg, J-M.: Genome sequencing: a systematic review of health economic evidence. Health economics review **3**(1), 29 (2013). doi: 10.1186/2191-1991-3-29.
31. Götze, U., Northcott, D., Schuster, P.: Investment appraisal. Methods and models. Springer texts in business and economics
32. Illumina, Inc.: cBot (2015). http://www.illumina.com/products/cbot.html. Assessed 17 March 2015
33. Holt, R.A., Jones, Steven J M: The new paradigm of flow cell sequencing. Genome research 18(6), 839–846 (2008). doi: 10.1101/gr.073262.107

34. QIAGEN: QIAamp DNA Blood Mini Kit (2016). https://www.qiagen.com/de/shop/sample-technologies/dna/dna-preparation/qiaamp-dna-blood-mini-kit#orderinginformation. Assessed 01 March 2016
35. Meynert, A.M., Ansari, M., FitzPatrick, D.R., Taylor, M.S.: Variant detection sensitivity and biases in whole genome and exome sequencing. BMC bioinformatics **15**, 247 (2014). doi: 10.1186/1471-2105-15-247
36. Dewey, F.E., Pan, S., Wheeler, M.T., Quake, S.R., Ashley, E.A.: DNA sequencing: clinical applications of new DNA sequencing technologies. Circulation **125**(7), 931–944 (2012). doi: 10.1161/CIRCULATIONAHA.110.972828
37. Schlötterer, C., Tobler, R., Kofler, R., Nolte, V.: Sequencing pools of individuals - mining genome-wide polymorphism data without big funding. Nature reviews. Genetics **15**(11), 749–763 (2014). doi: 10.1038/nrg3803
38. Kofler, R., Schlötterer, C.: A guide for the design of evolve and resequencing studies. Molecular biology and evolution **31**(2), 474–483 (2014). doi: 10.1093/molbev/mst221
39. McCourt, C.M., McArt, D.G., Mills, K., Catherwood, M.A., Maxwell, P., Waugh, D.J., Hamilton, P., O'Sullivan, J.M., Salto-Tellez, M.: Validation of next generation sequencing technologies in comparison to current diagnostic gold standards for BRAF, EGFR and KRAS mutational analysis. PloS one **8**(7), e69604 (2013). doi: 10.1371/journal.pone.0069604
40. Karow, J.: In Sequence 2013 Survey: Illumina Pulls Further Ahead, Interest in Oxford Nanopore Remains High (2014)
41. Studt, T,: Innovations Drive Rapid NGS Growth. Lower costs, high throughput and enhanced accuracies provide next-generation sequencing users with enhanced medical information. (2015)
42. PHG Foundation: PHG Foundation: Next steps in the sequence. The implications of whole genome sequencing for health in the UK, Cambridge (2011). http://www.phgfoundation.org/file/10363/. Assessed 23 April 2015
43. National Human Genome Research Institute: Genetic Discrimination (2014). http://www.genome.gov/10002077. Assessed 23 April 2015
44. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. Journal of clinical oncology: official journal of the American Society of Clinical Oncology **21**(12), 2397–2406 (2003). doi: 10.1200/JCO.2003.03.189
45. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. European journal of human genetics: EJHG **18**(12), 1271–1273 (2010). doi: 10.1038/ejhg.2010.129

Appendix

Table 5 Effects of workload differentiation at a 30-times coverage

Workload	Genomes per year		Type of costs	Cost (in €)	
	HiSeq 2500	HiSeq Xten		HiSeq 2500	HiSeq Xten
100%	608	19,456	Material	2,848.08	781.58
			Acquisition	387.91	159.90
			Maintenance	97.61	33.10
			Total run	**3,333.60**	**974.58**
90%	547	17,510	Material	2,848.08	781.58
			Acquisition	431.17	177.67
			Maintenance	108.49	36.78
			Total run	**3,387.74**	**996.03**
80%	486	15,564	Material	2,848.08	781.58
			Acquisition	485.29	199.89
			Maintenance	122.11	41.38
			Total run	**3,455.48**	**1022.85**
70%	425	13,619	Material	2,848.08	781.58
			Acquisition	554.94	228.44
			Maintenance	139.64	47.29
			Total run	**3,542.66**	**1057.31**
60%	364	11,673	Material	2,848.08	781.58
			Acquisition	647.94	266.52
			Maintenance	163.04	55.17
			Total run	**3,659.06**	**1103.27**

Table 6 Effects of coverage differentiation at a platform utilization of 80%

Coverage rate	Genomes per year		Type of costs	Cost (in €)	
	HiSeq 2500	HiSeq Xten		HiSeq 2500	HiSeq Xten
10×	1459	46,694	Material	969.41	280.58
			Acquisition	161.65	66.63
			Maintenance	40.68	13.79
			Total run	**1,171.74**	**361.00**
15×	972	31,129	Material	1,439.08	405.83
			Acquisition	242.64	99.94
			Maintenance	61.06	20.69
			Total run	**1,742.78**	**526.46**
30×	486	15,564	Material	2,848.08	781.58
			Acquisition	485.29	199.89
			Maintenance	122.11	41.38
			Total run	**3,455.48**	**1,022.85**
60×	243	7,782	Material	5,666.08	1,533.08
			Acquisition	970.58	399.78
			Maintenance	244.22	82.75
			Total run	**6,880.88**	**2,015.61**
75×	194	6,225	Material	7,075.08	1,908.83
			Acquisition	1,215.72	499.77
			Maintenance	305.91	103.45
			Total run	**8,596.71**	**2,512.05**

Modul 2

Ganzgenomsequenzierung in der deutschen Versorgung: Ökonomische Auswirkungen eines Einsatzes in ausgewählten Anwendungsgebieten

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Ganzgenomsequenzierung in der deutschen Versorgung - Ökonomische Auswirkungen eines Einsatzes in ausgewählten Anwendungsgebieten

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Zusammenfassung

Hintergrund: Der Einsatz von Whole Genome Sequencing (WGS) wird in der klinischen Versorgung vermehrt diskutiert. Aufgrund der begrenzten Ressourcen im Gesundheitswesen sind Budget-Impact Analysen notwendig, um die potentiellen Auswirkungen eines Einsatzes von WGS abschätzen zu können.

Ziel der Arbeit: Die ökonomischen Auswirkungen eines Einsatzes von WGS im Rahmen eines bevölkerungsweiten Screenings, Neugeborenenscreenings und zur diagnostischen Untersuchung von Tumorpatienten wurden evaluiert.

Methoden: Eine Kostenanalyse von WGS entlang eines qualitätsgesicherten Prozesses am Deutschen Krebsforschungszentrum (DKFZ) stellt die Basis dieser Analyse dar. Kennzahlen des GKV-Spitzenverbandes, des Bundesministeriums für Gesundheit und des Robert-Koch-Institutes bilden die Datengrundlage der untersuchten Szenarien.

Ergebnisse und Diskussion: Ein bevölkerungsweites Screening würde die GKV-Ausgaben im Jahr 2013 knapp um den 2,5-fachen Faktor erhöhen. WGS als Neugeborenscreening würde hingegen 2,63 Mrd. Euro verursachen und zu einer Ausgabensteigerung von 1,44% führen. Für eine Analyse aller Tumorpatienten müssten etwa 0,84 Mrd. Euro aufgewendet werden, was einen Ausgabenanstieg von 0,46% entspricht. Unberücksichtigt von möglichen Einsparpotentialen, führt die alleinige Betrachtung der Durchführungskosten von WGS in allen Szenarien zu steigenden Kosten. Im Hinblick auf die aktuellen Kosten ist vor allem der Einsatz von WGS als Bevölkerungsscreening nicht finanzierbar. WGS kann eine Vielzahl an deterministischen Befunden zu generieren, wofür z.T. noch keine Behandlungen existieren. Ein bevölkerungsweiter Einsatz scheint daher nicht realistisch und eine Kostenerstattung sollte nur an Indikationen gebunden sein, bei welchen eine klare Evidenz hinsichtlich des diagnostischen Nutzens vorliegt.

Schlüsselwörter: Ganzgenomsequenzierung; Budget-Impact-Analyse; Screening; Neugeborenenscreening; Onkologie; Genetische Diagnostik

Abstract

Background: The diagnostic use of Whole Genome Sequencing (WGS) is a growing issue in medical care. Due to the limited resources in Public Health Service budget-impact analysis are necessary prior to implementation.

Objective: Budget-impact analysis for a population-wide screening, a WGS of all newborns and diagnostic investigation of tumor patients in different oncologic indications were evaluated.

Methods: A cost analysis of WGS based on a quality-assured process chart for WGS at the German Cancer Research Center (DKFZ), Heidelberg, constitutes the basis for this evaluation. Data from the National Association of Statutory Health Insurance Funds, the Federal Ministry of Health and the Robert-Koch-Institute, Berlin, were used for calculations of specific clinical applications.

Results and discussion: A population-based screening would lead to an approximately 2.5-fold increase of expenses of statutory health insurance in 2013. In contrast WGS in newborn screening leads to a lower burden (€ 2.63 Billion) and to an increase of total expenditure by 1.44%. Cost of approximately € 0.84 Billion would be caused by sequencing of all tumor patients, which corresponds 0.46% of total expenditures. Independent of potential savings leads the application of WGS in all scenarios to increasing costs. With regard to the actual execution costs the use of WGS especially in a population-based screening is not fundable. WGS has the potential to generate a large number of deterministic findings. Partly, there are no treatment options for these. Hence, a population-based screening does not seem to be realistic and limitation of indications, in which WGS has proven medical evidence, is necessary.

Keywords: Whole Genome Sequencing, Budget-impact-analyses, screening; newborn screening, oncology, genetic diagnostics

Hintergrund

Im Jahr 2001 war der diagnostische Einsatz von Whole Genome Sequencing (WGS) aufgrund von Durchführungskosten in Höhe von ca. 100 Mio. US-Dollar pro Genom noch undenkbar [1]. Durch den technologischen Fortschritt konnten jedoch in den letzten Jahren erhebliche Zeit- und Kostenreduktionen in der Durchführung von WGS erzielt werden [2]. Als zentrales Werkzeug von Diagnostik und Therapie gewinnen genetische Analysen im Zeitalter der personalisierten Medizin immer mehr an Bedeutung.

Genetische Analysen (WGS, Genpanelsequenzierungen, Exomsequenzierungen (Whole Exome Sequencing (WES)) und die Sequenzierung einzelner Gene) können anhand ihres Analyseumfangs bzw. ihrer Sequenzierungsbreite differenziert werden [3]. Während sich WGS auf die Sequenzierung der Gesamtheit der Nukleotidsequenzen aller 23 Chromosomenpaare richtet, zielt WES auf die Analyse der kodierenden Genabschnitte aller Proteinmoleküle, Panelsequenzierung auf die Untersuchung von Genabschnitten und die Sequenzierung einzelner Gene auf die gezielte Analyse von krankheitsverursachenden Genen ab [4]. Da im Rahmen einer WGS alle ca. 3 Mrd. Basenpaare des humanen Genoms sequenziert werden, stellt WGS demzufolge auch die umfangreichste genetische Analyse dar [5].

Die wesentlichen versorgungsrelevanten Potentiale werden im Einsatz von WGS zu diagnostischen und prädiktiven Zwecken gesehen. Genetische Analysen können auf molekularer Basis die Erkrankungsursache identifizieren und somit eine genaue Diagnosestellung ermöglichen [3]. Dies hat vor allem bei Erkrankungen mit unbekanntem Ursprung eine erhebliche Relevanz. WGS beschränkt sich im Gegensatz zu WES nicht auf die kodierenden Genabschnitte und damit auf lediglich 1% des humanen Genoms [6]. Zwar sind Schätzungen zufolge 85% der krankheitsverursachenden Mutationen in diesen Abschnitten lokalisiert [7], jedoch können Mutationen und Kopienzahlvariationen (Copy Number Variations (CNVs)) außerhalb dieser Genabschnitte durch WES nicht erfasst werden. Dies birgt die Gefahr, dass erkrankungsrelevante Informationen nicht identifiziert oder seltene Varianten übersehen werden können.

Neben der diagnostischen Anwendung kann WGS auch zur Früherkennung von Risikopatienten eingesetzt werden [8]. In dieser Anwendungsmöglichkeit wird das entscheidend Neue gesehen: Der Einsatz von WGS zu prädiktiven Zwecken. WGS kann als Screeninginstrument eine Vielzahl von prädiktiven Befunden generieren. Beim Screening unterziehen sich Risikopatienten oder asymptomatische Personen aufgrund der Vorgeschichte, Familienanamnese oder lediglich aus Interesse einer genetischen Analyse, um Kenntnis über bis dato unbekannte Erkrankungen oder Dispositionen zu erlangen. Je umfassender eine genetische Analyse ist, desto größer ist das

prädiktive Potential bzw. die Wahrscheinlichkeit Dispositionen zu entdecken. Dies birgt gleichermaßen Chancen und Risiken: Auf der einen Seite können, sofern vorhanden, frühzeitig Präventions- und Therapiemaßnahmen eingeleitet werden, welche sowohl auf die positive Beeinflussung der Erkrankungsschwere und den Verlauf einer Erkrankung als auch auf die Verhinderung einer Erkrankungsmanifestation abzielen können [9]. Auf der anderen Seite bergen prädiktive und nicht-intendierte Befunde (sog. incidental findings) [10] auch die Gefahr, angstauslösendes Wissen hervorzurufen und somit negative Lebensqualitätseffekte zu bedingen. Der verängstigte Patient wird zum gesunden Kranken [11] und steigert seine Leistungsinanspruchnahme [12]. Die subjektive „Erkrankungsangst", erweitert die ursprüngliche Indikation [13] und kann somit zu höheren Folgekosten in den Bereichen Prävention und Therapie führen. Aktuell können jedoch weder die damit verbundenen Folgekosten abgeschätzt noch die klinische Relevanz derartiger Zufallsbefunde für viele Anwendungsgebieten eindeutig bestimmt werden.

Unabhängig von den potentiellen versorgungsrelevanten Vorteilen ist die Finanzierbarkeit und Kosteneffektivität von WGS von großer Relevanz. Die Entscheidung über den Analyseumfang (einzelne Gene, Genpanel, WES oder WGS) wird zukünftig wahrscheinlich nicht nur von der Fragestellung, sondern auch von den Kostenentwicklungen der jeweiligen Analyseart beeinflusst. Aktuell ist eine Anwendung weniger umfassender genetischer Analysen kostengünstiger und scheint daher, sofern hierdurch kein deutlicher Patientennutzen bedingt wird, u.a. aus ökonomischer Perspektive angemessener. Jedoch werden die Kostenreduktionen bei WGS zukünftig deutlich stärker ausfallen [14], wodurch sich im Zeitverlauf das Kostenniveau angleichen könnte. Diese erwarteten Kostenreduktionen und die Limitationen weniger umfassender genetischer Analysen führen zur Annahme, dass WGS im klinischen Setting zukünftig an Bedeutung zunehmen wird [15].

In dieser Analyse wird die Budgetwirkung in einem indikationsspezifischen (onkologisches Setting [16]) und eines indikationsunabhängigen Einsatzes (bevölkerungsweites Screening [17] und Neugeborenenscreening [18]) untersucht. Neben den Nutzendiskussionen in den jeweiligen Einsatzszenarien ließ der Mangel an validen Kostenstudien für WGS [19] bisher keine Aussage über die potentiellen finanziellen Auswirkungen einer Implementierung von WGS im diagnostischen Leistungsspektrum zu. Eine vorangegangene Studie zur Evaluation der Durchführungskosten von WGS stellt die Basis der vorliegenden Budget-Impact-Analyse dar.

Budget-Impact-Analysen als Entscheidungsinstrument

In Anbetracht der steigenden Kosten im Gesundheitswesen sind Budget-Impact-Analysen ein wichtiges Instrument, um die Bezahlbarkeit von medizinischen Interventionen abschätzen zu

können. Die Ermittlung des Budget-Impacts für die Gesetzliche Krankenversicherung (GKV) in Deutschland hängt sowohl von den Durchführungskosten einer WGS als auch von den konkreten Anwendungsgebieten bzw. der Anzahl der zu untersuchenden Patienten ab. Für die Gesamtzahl der potentiellen Patienten des jeweiligen Indikations- bzw. Anwendungsgebietes können potentiell anfallende Kosten prognostiziert werden. In eine Budget-Impact-Analyse können u.a. die zu erwartenden Kosten für die Durchführung, populationsbezogene Parameter der spezifischen (potentiellen) Anwendungsgruppe, Angaben zur Bevölkerungsentwicklung, Marktverschiebungen aufgrund von zusätzlichen Fallzahlen und Substitutionseffekte einfließen [20]. Da eine Kalkulation des Budget-Impacts dazu dienen kann, die Kostenträger bei der Entscheidungsfindung bezüglich möglicher Einsatzgebiete zu unterstützen, werden nachfolgend die finanziellen Auswirkungen in zwei potentiellen Anwendungsgebieten aufgezeigt.

Kosten von WGS

In einer vorangegangenen Studie wurden die Durchführungskosten einer WGS im deutschen Versorgungssetting evaluiert [21]. Der primäre Gegenstand dieser Untersuchung war eine Abbildung von Kosten, die im Zusammenhang mit der Durchführung einer WGS entstehen. Entlang eines qualitätsgesicherten Prozessablaufes am Deutschen Krebsforschungszentrum in Heidelberg (DKFZ) konnten die essentiellen Kostenpositionen des Prozesses einer WGS identifiziert, quantifiziert und monetär bewertet werden. Im Mittelpunkt dieser Erhebung standen die medizinischen Einzelkosten einer WGS. Gemeinkosten wurden aufgrund der fehlenden Zurechenbarkeit nicht inkludiert. Eine Ausnahme stellen jedoch die Anschaffungs- und Wartungskosten der Sequenzierungsplattform dar. Eine umfassende Erhebung aller Gemeinkosten und die additive Berücksichtigung der Datenspeicherungskosten würden grundsätzlich mit einer Kostensteigerung einhergehen. Die evaluierten Kosten in Höhe von 3.858,06 € pro WGS sind ein wesentlicher Ausgangspunkt für weiterführende Analysen.

Potentielle Einsatzgebiete von WGS: Grundlegende Annahmen und ökonomische Auswirkungen

In dieser Analyse wird der Einsatz von WGS zu diagnostischen, prädiktiven oder prognostischen Zwecken als Add-On-Technologie definiert. Eine Anwendung von WGS ersetzt somit keine bestehende Maßnahme und Substitutionseffekte bleiben unberücksichtigt. Die Anwendung von WGS führt damit zu additiven diagnostischen Kosten und schließlich zu einer Erhöhung des Ausgabenvolumens in der GKV. Als grundlegende Kalkulations- und Referenzbasis werden die reinen Leistungsausgaben (ohne Nettoverwaltungskosten und sonstige Aufwendungen) der GKV des Jahres 2013 in einer Höhe von 182,75 Mrd. Euro verwendet [22]. Es wurde eine Art

flächendeckender Ansatz gewählt. Dieser liefert eine erste Einschätzung zum maximal aufzuwendenden Finanzierungsvolumen eines Einsatzes von WGS im diagnostischen Leistungsspektrum der GKV. Um die ökonomischen Auswirkungen einer Implementierung von WGS darzustellen, wurden Budget-Impact-Analysen für drei potentiell denkbare Einsatzszenarien durchgeführt.

Ökonomische Auswirkungen einer indikationsspezifischen Anwendung von WGS

Szenario 1- Einsatz in der Onkologie: WGS kann im onkologischen Setting zu diagnostischen, prädiktiven und prognostischen Zwecken eingesetzt werden. Im prädiktiven Kontext kann WGS zur Identifikation von Mutationen in Proto-Onkogenen oder Tumorsuppressorgenen, die ein erhöhtes Risiko für das Auftreten von Tumoren bedingen (Bsp. BRCA I und BRCA II für Mamma- und Ovarialkarzinome), eingesetzt werden und Informationen über das Therapieansprechen liefern [22]. Im Rahmen des prognostischen Einsatzes kann WGS molekulargenetische Charakterisierungen (z.B. Aggressivität und biologisches Verhalten der Tumorzellen) einer Krebserkrankung ermöglichen [23] und als diagnostisches Instrument eine genaue Charakterisierung bzw. Diagnosestellung ermöglichen [6]. Das Ziel des Nationalen Centrums für Tumorerkrankungen (NCT), ab dem Jahr 2015 alle Tumorpatienten einer Erbgutanalyse zu unterziehen, verdeutlicht die Relevanz von WGS im onkologischen Setting [24].

Die indikationsspezifische Analyse richtet sich auf Versicherte mit bereits manifestierter Erkrankung. Bei einem Tumorpatienten kann WGS sowohl prädiktive, diagnostische und prognostische Informationen hinsichtlich Erkrankungsspezifika, Krankheitsverlauf und Therapieoptionen als auch Aussagen zur Wirksamkeit von stratifizierten Pharmakotherapien liefern. Im Rahmen der Studienkonzeption wird WGS grundsätzlich als Add-on Technologie definiert. Folglich werden keine bestehenden diagnostischen Instrumente, wie bspw. genetische Biomarkertestverfahren, substituiert. Die ökonomischen Auswirkungen von WGS werden sowohl in Bezug auf die Gesamtanzahl der onkologischen Neuerkrankungen als auch geschlechtsspezifisch innerhalb der zehn häufigsten Neuerkrankungsgruppen dargestellt. Zudem werden die Gesamtkosten einer Implementierung in ein Verhältnis zu den Ausgaben der gesetzlichen Krankenversicherung (GKV) gesetzt. Die Datenbasis in diesem Szenario bilden epidemiologische Zahlen des Robert-Koch Institutes aus dem Jahr 2009/2010 [26] und Kennzahlen des GKV-Spitzenverbandes zu den Leistungsausgaben aus dem Jahr 2013 [22].

Eine genetische Analyse aller Tumorpatienten innerhalb der zehn häufigsten onkologischen Indikationen hätte im Betrachtungsjahr 2013 Kosten in Höhe von 0,84 Mrd. Euro verursacht. Diese Kosten hätten etwa 0,46% der Leistungsausgaben der GKV (Tabelle 1) entsprochen. Die Erkrankungshäufigkeiten divergieren geschlechterspezifisch. Erkrankungen der Brustdrüse waren bei Frauen mit einer absoluten Anzahl von 17.466 Fällen am häufigsten im onkologischen

Setting verbreitet. Für den Einsatz von WGS innerhalb dieser Indikationsgruppe hätten 67 Mio. Euro aufgewendet werden müssen. Bei Männern stellt Lungenkrebs mit einer Fallzahl von 29.381 Lungenkrebs die häufigste onkologische Erkrankung dar. In dieser Indikation hätte die Sequenzierung aller Erkrankten Ausgaben in Höhe von 113 Mio. Euro verursacht.

Tabelle 1 Kosten des Einsatzes von WGS in der Onkologie

Frauen				Männer		
Erkrankung		Häufigkeit	Kosten in €	Erkrankung	Häufigkeit	Kosten in €
Gesamt		100.403	387.360.798,00	Gesamt	117.855	454.691.661,00
Prozentualer Anstieg der Kosten von WGS für die Gesamtheit der onkologischen Patienten an den Leistungsausgaben der GKV im Jahr 2013			0,2119 %	Prozentualer Anteil der Kosten von WGS für die Gesamtheit der onkologischen Patienten an den Leistungsausgaben der GKV im Jahr 2013		0,2488 %
1	Brustdrüse	17.466	67.384.876,00	Lunge	29.381	113.353.661,00
2	Lunge	13.627	52.573.783,60	Darm	13.489	52.041.371,30
3	Darm	12.510	48.264.330,60	Prostata	12.676	48.904.768,60
4	Bauchspeicheldrüse	7.950	30.671.577,00	Bauchspeicheldrüse	7.537	29.078.198,20
5	Eierstöcke	5.599	21.601.277,90	Magen	5.777	22.288.012,60
6	Magen	4.400	16.975.464,00	Leber	4.856	18.734.739,40
7	Leukämien	3.304	12.747.030,20	Leukämien	3.942	15.208.472,50
8	Non-Hodgkin-Lymphome	2.921	11.269.393,30	Speiseröhre	3.837	14.803.376,20
9	Zentrales Nervensystem	2.559	9.872.775,54	Mundhöhle und Rachen	3.816	14.722.357,00
10	Leber	2.534	9.776.324,04	Harnblase	3.631	14.008.615,90

Ökonomische Auswirkungen von indikationsunabhängigen Anwendungen

Szenario 2- Bevölkerungsweites Screening: Für dieses als hypothetisch einzustufendes Anwendungsszenario wurden folgende Annahmen getroffen: 1. Jedem Versicherten steht es frei eine WGS zu prädiktiven Zwecken durchführen zu lassen; 2. Die Kostenerstattung wird durch die GKV sicherstellt; 3. Jeder Versicherungsnehmer kann einmalig diese diagnostische Leistung in Anspruch nehmen und 4. Da keine bestehenden genetischen Screeningangebote substituiert werden findet der Einsatz von WGS als Add-on-Technologie statt. Die Berechnung des Budget-Impacts wird für die Gesamtanzahl der GKV-Versicherten durchgeführt und erfolgt mittels der Kennzahlen des Bundesministeriums für Gesundheit [27] und des GKV-Spitzenverbandes des Jahres 2013 [22]. Die für dieses indikationsunabhängige Screening aufzuwendenden Ausgaben werden sowohl prozentual im Verhältnis zu den Gesamtausgaben als auch an den Ausgaben für Früherkennungsmaßnahmen dargestellt (Tabelle 2). Basierend auf der Annahme, dass eine WGS nur einmal im Leben durchgeführt werden muss, entstehen für die GKV einmalige Durchführungskosten pro Mitglied. Bei einer retrospektiven Betrachtung des Jahres 2013 hätte die Durchführung eines bevölkerungsweiten Screenings ohne Indikationsbegrenzung im Versichertenkollektiv der GKV ein Ausgabenvolumen von 269,50 Mrd. Euro verursacht. Im Betrachtungsjahr hätte dies faktisch zu etwa 2,5-fach so hohen GKV-Leistungsausgaben geführt. Werden die Kosten dem Leistungsbereich der Früherkennungsmaßnahmen zugeordnet, wäre dies mit einem Anstieg von 13.019 % innerhalb dieses Ausgabenbereichs einhergegangen.

Szenario 3- Screening aller Neugeborenen: Im diesem Szenario wird angenommen, dass alle Neugeborenen einer WGS unterzogen werden. In dieser Analyse wird das im Regelleistungskatalog der GKV verankerte „erweiterte Neugeborenenscreening" von WGS nicht substituiert. Als Datengrundlage werden die Geburtenzahlen des Statistischen Bundesamts und die Leistungsausgaben der GKV des Jahres 2013 verwendet [28]. Für den Einsatz von WGS im Rahmen des Neugeborenenscreenings hätten die Kostenträger im Jahr 2013 für 682.069 Neugeborene Ausgaben in Höhe von 2,63 Mrd. Euro aufwenden müssen. Dies hätte einer 1,44%-Steigerung der Leistungsausgaben entsprochen. Werden die Kosten für das genetische Neugeborenenscreening dem Leistungsbereich der Früherkennungsmaßnahmen zugeordnet, hätte dies einem Ausgabenanstieg von 127% innerhalb dieses Leistungsbereichs verursacht (Tabelle 2).

Tabelle 2 Kosten des Einsatzes von WGS in indikationsunabhängigen Screeningprogrammen

Bezugsgrößen	**Anzahl/ Kosten in Mrd. €**
Anzahl der Neugeborenen (2015)	737.575
Leistungsausgaben der GKV (2015)	202,05
Gesamtkosten für Früherkennungsmaßnahmen der GKV (2015)	2,18
Auswirkungen/ Kosten (-anstieg)	**Kosten in Mrd. €/ Anstieg in %**
Gesamtkosten für das Neugeborenenscreening (in Mrd.)	2,85
Anstieg der Leistungsausgaben	1,41
Anstieg der Kosten für Früherkennungsmaßnahmen	130,73

Diskussion

Während genetische Analysen vor einigen Jahren noch primär in der Humangenetik, Kinderheilkunde und Gynäkologie eingesetzt wurden [29], finden diese inzwischen auch vermehrt Anwendung in anderen Bereichen, wie z.B. der Kardiologie, Immunologie und Onkologie. Die Anwendungsmöglichkeiten von genetischen Analysen erweitern sich kontinuierlich und auch die stetig sinkenden Kosten lassen den Schluss zu, dass genetische Analysen in naher Zukunft ein fester Bestandteil sämtlicher Versorgungsbereiche sein könnten.

Auch wenn der potentielle Nutzen eines Einsatzes von WGS im Einzellfall erheblich sein kann, muss geprüft werden, ob WGS nach den Leistungskriterien der GKV als wirtschaftlich, notwendig und zweckmäßig (§ 12 SGB V) einzustufen ist. Im Vergleich zu anderen Diagnostika sind die aktuellen Durchführungskosten von WGS in Höhe von ca. 3.900 € noch immer als relativ hoch einzuschätzen. Unabhängig von den Durchführungskosten, sollten jedoch auch die potentiellen Kosteneinsparungen betrachtet werden, welche durch vermiedene Folgekosten (schnellere Diagnosefindung, frühzeitige Intervention etc.) erzielt werden und eine erhebliche ökonomische Relevanz haben können.

Als *indikationsspezifisches Einsatzgebiet* für genetische Analysen kommt der Onkologie die weitreichendste Bedeutung zu. Die Entstehung von Krebs ist ein multifaktorielles Zusammenspiel, bei welchen sowohl genetische als auch epigenetische Faktoren eine Rolle spielen [30]. In 90% aller bekannten krebsassoziierten Gene treten somatische (also sporadisch auftretende) Mutationen auf, 20% zeigen Keimbahnmutationen, woraus folgt dass in 10% beide Mutationen vorkommen [31]. Dabei stellt WGS eine Möglichkeit dar, diese genetischen Veränderungen zu identifizieren. Die Relevanz des prädiktiven Potentials, welches auf ein spezifisches Risikoprofil und ein erhöhtes Krankheitsrisiko hinweisen kann, wurde durch die Umsetzungsempfehlung für risikoadaptierte Früherkennungsprogramme des Nationalen Krebsplan gestärkt. Hierbei sollen Patienten mit einem erhöhten Erkrankungsrisiko durch einen zweistufigen Filtertest (nach der Identifikation einer familiären genetischen Belastung) einen Zugang zur genetischen Analyse erhalten, um das Morbiditäts- und Mortalitätsrisiko zu senken [32]. Die Identifikation von Risiko-Genen schafft die Chance einer gezielten Prävention in diesen Hochrisikogruppen [33]. Die Analyse des Tumorgenoms ermöglicht eine Identifikation von Erbgutveränderungen und somit eine konkrete Diagnosestellung. Da sich Malignome nicht nur zwischen einzelnen Individuen unterscheiden, sondern selbst innerhalb des Tumors erhebliche Divergenzen aufweisen [34], kommt genetischen Analysen im onkologischen Setting eine große diagnostische Relevanz zu. Aufgrund dieses Wissens ist es den behandelnden Ärzten möglich, therapeutische Interventionen entsprechend der Tumorcharakteristika einzuleiten. Genetische Analysen können zudem auch prognostische und prädiktive Informationen generieren, welche Aussagen über die Wahrscheinlichkeit des Therapieansprechens, die Entwicklung von unerwünschten Nebenwirkungen und den potentiellen Krankheitsverlauf liefern können. Vor allem in Hinblick auf die stratifizierte Medizin gewinnen genetische Analysen in der Onkologie kontinuierlich an Bedeutung.

Die ökonomischen Auswirkungen eines indikationsunabhängigen Einsatzes von WGS wurden sowohl für ein *Bevölkerungs- als auch Neugeborenscreening* untersucht. In beiden Szenarien bleibt der Einsatz von WGS als ein Instrument zur Krankheitsfrüherkennung zu diskutieren. Die 1968 von Wilson und Jungner im Auftrag der WHO definierten Grundsätze zum Screening [35] (Vorliegen eines wichtigen Gesundheitsproblems, Testbedingungen (z.B. Eignung des Tests), Kenntnis über den Krankheitsverlauf, die Identifikation in einem latenten oder frühen symptomatischen Stadium und die Behandlungsfähigkeit etc.) erfuhren vor allem in Hinblick auf Besonderheiten des genomischen Zeitalters in den letzten Jahren eine Anpassung. Aufgrund der Möglichkeiten der Detektion einer Erkrankung vor der phänotypischen Manifestation werden u.a. Forderungen nach einer Definition einer Zielindikation, der wissenschaftlichen Evidenz der Effektivität des Screeningprogramms, Qualitätssicherung zur Minimierung der potentiellen Screeningrisiken etc. zu diesen Kriterien laut [36]. Das Wissen über eine Disposition bzw.

potentielle Erkrankungsmanifestation versetzt die Betroffenen bzw. deren behandelnden Ärzte in die Lage, vor allem Maßnahmen der primären (z.B. gesunde Lebensweise) und sekundären (z.B. Krankheitsfrüherkennung) Prävention durchzuführen [37]. Dies setzt allerdings voraus, dass für die jeweiligen Dispositionen auch Behandlungsmöglichkeiten existieren. Die frühzeitige Identifikation einer Disposition kann eine schnelle Einleitung von präventiven oder therapeutischen Maßnahmen ermöglichen, womöglich einen Krankheitsausbruch verhindern [38] und somit Folgekosten bzw. Versorgungskosten senken [39]. Als Bespiel fungiert hierbei die frühzeitige Detektion der Disposition von Mukoviszidose in einem prä-pathologischen Stadium. Zwar ist diese Erkrankung nicht heilbar, jedoch kann eine frühzeitige Intervention die Krankheitsanzeichen verringern und zu einer Steigerung der Lebensqualität und -erwartung beitragen [40].

Die Anwendung von WGS im Rahmen eines *bevölkerungsweiten Screenings* würde Kosten in Höhe von 269,50 Mrd. Euro verursachen und in der GKV zu einer Ausgabensteigerung von 147 % führen. Demnach ist ein Screening ohne Indikationsbegrenzung zu aktuellen Durchführungskosten nicht finanzierbar. Grundsätzlich kann diesem Szenario ein eher hypothetischer Charakter zugeschrieben werden. Ein allgemeines Screening zu prädiktiven Zwecken zielt primär auf die Detektion von Keimbahnmutationen ab. Da bei genetisch vererbbaren Erkrankungen vor allem eine frühzeitige Detektion vorteilhaft sein kann, stellt sich bei der Diskussion um den Einsatz von WGS im Rahmen eines bevölkerungsweiten Screenings die Frage nach der medizinischen Notwendigkeit bzw. nach der Versorgungsrelevanz. Eine frühzeitige Detektion von genetischen Dispositionen könnte jedoch durch ein Neugeborenenscreening erzielt werden. Demnach kann u.a. dieses Szenario als ein zukünftig realistisch denkbares Anwendungsgebiet eingestuft werden. Zudem würden auch im Gegensatz zum bevölkerungsweiten Screening die finanziellen Ausgaben für die GKV in Höhe von 2,63 Mrd. Euro für ein *Neugeborenenscreening* deutlich geringer ausfallen. Das derzeitige Neugeborenenscreening zählt dem Gendiagnostikgesetz nach zu den genetischen Reihenuntersuchungen und seit dem Jahr 2005 wird das „erweiterte Neugeborenenscreening“ als Regelleistung der GKV erstattet [41]. Eine Erweiterung des Neugeborenenscreenings könnte ein potentielles Anwendungsgebiet von WGS darstellen. Ob jedoch die als Goldstandart geltende Tandem-Massenspektrometrie (TMS) durch WGS ergänzt werden kann, ist unter diversen Aspekten zu betrachten. TMS hat die Identifikation von 14 Stoffwechsel- und Hormonkrankheiten zum Gegenstand und zielt lediglich Detektion von behandelbaren angeborenen Endokrinopathien und Stoffwechseldefekten ab [42]. Im Gegensatz dazu können durch WGS eine Vielzahl von prädiktiven genetischen Befunden generiert werden, für welche z.T. keine Behandlungsmöglichkeiten existieren. Bei den genetischen Analyseergebnissen handelt es sich um probabilistische Aussagen, bei welchen zum Untersuchungszeitpunkt in den

meisten Fällen nicht eindeutig bestimmt werden kann, ob im Leben des Säuglings jemals zu einer phänotypischen Manifestation der Dispositionen kommen wird [43]. Unabhängig davon können diese genetischen Informationen nicht nur einen weitreichenden Einfluss auf das Leben des getesteten Säuglings, sondern auch auf dessen Familienangehörige haben. Wird eine genetische Mutation beim Neugeborenen entdeckt, besteht die Möglichkeit, dass ein Elternteil ein heterozygoter Merkmalsträger ist [44].

Grundsätzlich ist der Nutzen dieser Intervention schwierig zu bewerten, da aufgrund der Analyseergebnisse von WGS auch negative Effekte für das Leben des Getesteten und dessen Angehörigen resultieren können [45]. Daher ist es unabdingbar den Nutzen von WGS weiter zu evaluieren, bevor WGS ins diagnostische Leistungsspektrum Einzug erhält. Genomweite Assoziationsstudien (GWAS) stellen hierbei ein essentielles Instrument zur weiteren Evidenzgenerierung dar. GWAS ermöglichen den Vergleich zwischen gesunden und erkrankten Populationsanteilen und tragen somit zur Identifizierung von Korrelationen zwischen genetischen veränderten Genabschnitten und spezifischen Krankheitsbildern bei [46]. Die Potentiale von genetischen Informationen sind in diesem Zusammenhang auch für die molekulargenetische Forschung enorm. Aus diesem Grund finanzierte die britische Regierung mit dem 100.000 Genomes Project, das auf die Sequenzierung breiter Bevölkerungsanteile abzielte, eines der größten DNA-Sequenzierungsprojekte aller Zeiten [47].

Einer breiten klinischen Anwendung stehen nicht nur die mit WGS verbundenen Kosten, rechtliche und ethische [48] sondern auch organisatorische bzw. strukturelle Hürden entgegen. Als ein Beispiel hierfür kann die Organisation und der gestiegene Aufwand der humangenetischen Beratung angeführt werden. Entsprechend des 2010 in Kraft getretenen Gendiagnostikgesetzes stellt die qualifizierte genetische Beratung (§ 10 GenDG) ein verpflichtendes Element im Prozess der genetischen Analyse dar. Im Hinblick auf die nicht-intendierten Befunde, welche über die primäre Indikation hinausgehen, gewinnt die genetische Beratung deutlich an Komplexität. Inwiefern dieser mit einer Implementierung von WGS gestiegene genetische Beratungsaufwand mit den aktuell verfügbaren zeitlichen und ökonomischen Kapazitäten sichergestellt werden kann, bleibt zu prüfen.

Während aus ökonomischer Sicht ein bevölkerungsweites Screeningprogramm derzeit abzulehnen ist, wäre losgelöst von ethischen und rechtlichen Fragen, eine Erweiterung des Neugeborenenscreenings um WGS zu rechtfertigen, sofern ein entsprechender Zusatznutzen nachgewiesen werden kann. Regelungen in Bezug auf die Rückmeldung der Befunde könnten sowohl in indikationsspezifischen als auch indikationsunabhängigen Anwendungsgebieten ein wichtiges Instrument der Ausgabenbegrenzung darstellen.

Die Konzeption der untersuchten Szenarien und die für die Berechnungen zugrundeliegende Kostenstudie stellen Limitationen dieser Studie dar. In der Evaluation der Durchführungskosten von WGS wurden bspw. Gemeinkosten, wie Strom, Wasser und Kosten der Datenspeicherung, aus der Erhebung exkludiert. Eine additive Berücksichtigung dieser Kosten würde zu einer Steigerung der Gesamtkosten und somit zu höheren Ausgaben innerhalb der betrachteten Szenarien führen. Ebenfalls haben die Annahmen der Szenarien einen Einfluss auf den Budget-Impact. Für die indikationsunabhängigen Anwendungen wurde unterstellt, dass sich alle Versicherten einer umfassenden Analyse bzw. dass alle Eltern ihr Neugeborenes einer WGS unterziehen. In der Versorgungsrealität ist dieser flächendeckende Ansatz eher unwahrscheinlich und demzufolge kann hier von einer deutlichen Überschätzung der Kosten ausgegangen werden. Diese Evaluation liefert jedoch eine erste Einschätzung des maximal aufzuwendenden Finanzierungsvolumens eines indikationsunabhängigen Einsatzes von WGS. Aufgrund der Annahme des Einsatzes von WGS als Add-on-Diagnostikum ist ebenfalls von einer Überschätzung der Kosten auszugehen. Genetische Analysen sind u.a. inzwischen vermehrt Bestandteil in der onkologischen Versorgung (bspw. prognostische Testungen auf die Wirksamkeit stratifizierter Therapien). WGS könnte diese somit grundsätzlich substituieren. In den drei untersuchten Einsatzgebieten wurde von einem Einsatz von WGS als Add-on-Technologie ausgegangen, da zum Untersuchungszeitpunkt keine validen Schätzungen bezüglich der tatsächlichen Anwendungshäufigkeit genetischer Analysearten identifiziert werden konnten. Weiterhin ist hier von diversen Kompensationseffekten auszugehen, welche eine endgültige Beurteilung der tatsächlichen Ausgabenbelastung erschweren. Die Stärke dieser Effekte ist primär von den Kostenentwicklungen im Bereich der Sequenzierungstechnologien abhängig. Somit stellen die Kosten für WGS und die darauf aufbauenden Budget-Impact-Analysen keine abschließenden Ergebnisse dar, sondern bedürfen einer kontinuierlichen Anpassung. Eine weitere Limitation ist in der Konzeption des onkologischen Szenarios zu sehen. Hierbei wurde lediglich von einer Sequenzierung aller Neuerkrankten ohne die Berücksichtigung von Rezidivfällen ausgegangen. Ein Einschluss von Rezidivpatienten würde mit einer Steigerung der Ausgaben im Betrachtungsjahr einhergehen.

Die ökonomische Betrachtung dieses innovativen Bereichs befindet sich noch in einer frühen Phase. Dementsprechend konnten im Rahmen der Bearbeitung weitere interessante Forschungsbedarfe identifiziert werden. Im onkologischen Bereich wäre z.B. eine nach der Untersuchungsintention (prädiktiver, prognostischer oder diagnostischer Kontext) differenzierte Kostenanalyse als auch eine Erhebung der Kosten, welche durch WGS von Risikopatienten entstehen, denkbar. In der vorliegenden Analyse wurde ein Inzidenzansatz in einem spezifischen Betrachtungsjahr untersucht. Eine mögliche Erweiterung dieser Analyse könnte in einem Prävalenzansatz mit einer additiven Berücksichtigung von Neuerkrankungen

und Rezidivfällen in den Folgejahren gesehen werden. Aufgrund der zum Untersuchungszeitpunkt verfügbaren Datenquellen konnten diese offenen Fragestellungen nicht adäquat abgebildet werden und stellen somit eine Ausgangsbasis für zukünftige Forschungsvorhaben dar.

Fazit:

Die ökonomische Evaluation der diskutierten potentiellen Einsatzgebiete von WGS verdeutlicht die Notwendigkeit einer Indikationsbegrenzung von WGS. Ein bevölkerungsweites Screening würde mit einer Steigerung der GKV-Leistungsausgaben von 147 % einhergehen. Dies zeigt, dass neben der aktuell fragwürdigen Relevanz für die medizinische Versorgung, ein Screenings der Gesamtbevölkerung vor allem auch aus der ökonomischen Perspektive abzulehnen ist. Hingegen kann der Einsatz von WGS in der onkologischen Versorgung und im Rahmen des Neugeborenenscreenings sowohl als zukünftig realistisch als auch ökonomisch vertretbar eingestuft werden. Da jedoch aktuell häufig z.T. noch keine Behandlungsmöglichkeiten für deterministische Befunde existieren, sollte die Kostenerstattung an Indikationen gebunden sein, für welche eine klare Evidenz im Hinblick auf den diagnostischen Nutzens vorliegt.

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Literatur

1. Wetterstrand KA (2016) DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP). www.genome.gov/sequencingcosts. Zugegriffen: 03. Februar 2016
2. Shendure J, Ji H (2008) Next-generation DNA sequencing. Nature biotechnology 26(10): 1135–1145. doi: 10.1038/nbt1486
3. Xue, Yu et al. (2014) Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. Genetics in medicine: official journal of the American College of Medical Genetics. doi: 10.1038/gim.2014.122
4. Deutscher Ethikrat (Hg.) (2013) Die Zukunft der genetischen Diagnostik - von der Forschung in die klinische Anwendung. Stellungsnahme. [s.n.], Berlin
5. Venter JC, Adams MD, Myers EW et al. (2001) The sequence of the human genome. Science (New York, N.Y.) 291(5507): 1304–1351. doi: 10.1126/science.1058040
6. Choi M, Scholl UI, Ji W et al. (2009) Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. Proceedings of the National Academy of Sciences of the United States of America 106(45): 19096–19101. doi: 10.1073/pnas.0910672106
7. Majewski J, Schwartzentruber J, Lalonde E, Montpetit A, Jabado N (2011) What can exome sequencing do for you? Journal of medical genetics 48(9): 580–589. doi: 10.1136/jmedgenet-2011-100223
8. Berg JS, Khoury MJ, Evans JP (2011) Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genetics in medicine: official journal of the American College of Medical Genetics 13(6): 499–504. doi: 10.1097/GIM.0b013e318220aaba
9. Happe K (2010) Prädiktive genetische Diagnostik als Instrument der Krankheitsprävention. Stellungnahme. Dt. Akad. der Naturforscher Leopoldina, Nat. Akad. der Wiss., Halle (Saale)
10. Green RC, Berg JS, Grody WW et al. (2013) ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genetics in medicine: official journal of the American College of Medical Genetics 15(7): 565–574. doi: 10.1038/gim.2013.73.
11. Hubbard R (1993) Predictive genetics and the construction of the healthy ill. Suffolk Univ Law Rev
12. Zerres K (2007) Diagnostik als Kostenfaktor: 97–108
13. Frank M, Gantner G, Molnár-Gabor F, Wiemann S (2014) Klinische Genomsequenzierung und der Umgang mit Zusatzbefunden im Spannungsfeld von ethisch-rechtlichen Voraussetzungen und ökonomischen Erwägungen. In: Frewer (Hg.) Jahrbuch Ethik in der Klinik (JEK) 7, Jahrbuch Ethik in der Klinik (JEK) 7, S 175–208
14. Belkadi A, Bolze A, Itan Y et al. (2015) Whole-genome sequencing is more powerful than whole-exome sequencing for detecting exome variants. Proceedings of the National Academy of Sciences of the United States of America 112(17): 5473–5478. doi: 10.1073/pnas.1418631112
15. Berlin-Brandenburgische Akademie der Wissenschaften (Hrsg.) (2013) Stellungnahme zu den neuen Sequenzierungstechniken und ihren Konsequenzen für die genetische Krankenversorgung. Berlin-Brandenburgische Akademie der Wissenschaften, Berlin
16. Chen K, Meric-Bernstam F (2015) Whole Genome Sequencing in Cancer Clinics. EBioMedicine 2(1): 15–16. doi: 10.1016/j.ebiom.2014.12.007
17. van El, Carla Geertruida, Pieters T, Cornel M (2012) Genetic screening and democracy: lessons from debating genetic screening criteria in the Netherlands. Journal of community genetics 3(2): 79–89. doi: 10.1007/s12687-011-0063-z
18. Bodian DL, Klein E, Iyer RK et al. (2016) Utility of whole-genome sequencing for detection of newborn screening disorders in a population cohort of 1,696 neonates. Genetics in medicine: official journal of the American College of Medical Genetics 18(3): 221–230. doi: 10.1038/gim.2015.111

19. Frank M, Prenzler A, Eils R, Graf von der Schulenburg, J-Matthias (2013) Genome sequencing: a systematic review of health economic evidence. Health economics review 3(1): 29. doi: 10.1186/2191-1991-3-29
20. Schöffski O, von der Schulenburg JM (2008) Gesundheitsökonomische Evaluationen, 3., vollst. überarb. Aufl. Springer, Berlin [u.a.]
21. Plöthner M, Frank M, von der Schulenburg JM Cost-Analysis for Whole Genome Sequencing in German clinical practice. Angenommen im European Journal for Health Economics. doi: 10.1007/s10198-016-0815-0
22. GKV-Spitzenverband (2015) Kennzahlen der gesetzlichen Krankenversicherung. http://www.gkv-spitzenverband.de/media/grafiken/gkv_kennzahlen/kennzahlen_gkv_2014_q4/GKV_Kennzahlen_Booklet_Q4-2014_300dpi_2015-03-26.pdf. Zugegriffen: 28. Mai 2015.
23. Smith KL, Isaacs C (2011) BRCA mutation testing in determining breast cancer therapy. Cancer journal (Sudbury, Mass.) 17(6): 492–499. doi: 10.1097/PPO.0b013e318238f579
24. Krebsinformationsdienst (2006) Molekularbiologische Diagnostik: Welche Informationen liefert sie? Forschung, Therapieplanung, Verlaufskontrolle. https://www.krebsinformationsdienst.de/grundlagen/molekularbiologie-informationen.php. Zugegriffen: 01. Juni 2015
25. Deutsches Krebsforschungszentrum und Dietmar Hopp Stiftung (2014) Individualisierte Krebsmedizin für jeden Patienten: Dietmar Hopp Stiftung unterstützt Initiative am Nationalen Centrum für Tumorerkrankungen (NCT) Heidelberg mit 15 Millionen Euro. https://www.dkfz.de/de/presse/pressemitteilungen/2014/dkfz-pm-14-24-Individualisierte-Krebsmedizin-fuer-jeden-Patienten.php. Zugegriffen: 05. Juli 2016
26. Robert Koch-Institut und Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (2013) Krebs in Deutschland 2009/2010, 9. Aufl., Berlin
27. Bundesministerium für Gesundheit (2015) Gesetzliche Krankenversicherung - Kennzahlen und Faustformeln -. http://bmg.bund.de/fileadmin/dateien/Downloads/Statistiken/GKV/Kennzahlen_Daten/KF2015Bund_Januar_2015.pdf. Zugegriffen: 28. Mai 2015
28. Statistisches Bundesamt Anzahl der Geburten in Deutschland von 1991 bis 2013. http://de.statista.com/statistik/daten/studie/235/umfrage/anzahl-der-geburten-seit-1993. Zugegriffen: 28. Mai 2015
29. Ärztekammer Berlin (2015) Gendiagnostikgesetz - Regelungen zu genetischen Untersuchungen und zur Qualifikation zur fachgebundenen genetischen Beratung im Zusammenhang mit genetischen Untersuchungen. https://www.aerztekammer-berlin.de/10arzt/30_Berufsrecht/10_Gesetzesaenderungen/54_Gendiagnostikgesetz.html. Zugegriffen: 30. Juni 2016
30. Krebsinformationsdienst (2011) Krebsentstehung. https://www.krebsinformationsdienst.de/grundlagen/krebsentstehung.php. Zugegriffen: 05. Juni 2016
31. Futreal PA, Coin L, Marshall M et al. (2004) A census of human cancer genes. Nature reviews. Cancer 4(3): 177–183. doi: 10.1038/nrc1299
32. Bundesgesundheitsministerium für Gesundheit (2012) Nationaler Krebsplan-Handlungsempfehlungen, Ziele und Umsetzungsempfehlungen
33. Deutsches Referenzzentrum für Ethik in den Biowissenschaften (2014) Prädiktive genetische Testverfahren. http://www.drze.de/im-blickpunkt/praediktive-genetische-testverfahren. Zugegriffen: 28. Mai 2015
34. Bördlein I (2013) Onkologie: Therapie im „Genzeitalter“. Deutsches Ärzteblatt(110): A-1858 / B-1638 / C-1608
35. Wilson, J.M.G. und Jungner, G. (1968) Principles and practice of screening for disease. http://apps.who.int/iris/bitstream/10665/37650/17/WHO_PHP_34.pdf. Zugegriffen: 30. Juni 2016

36. Andermann A (2008) Revisting wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ 86(4): 317–319. doi: 10.2471/BLT.07.050112
37. Bundesministerium für Gesundheit (2015) Prävention. http://www.bmg.bund.de/glossarbegriffe/p-q/praevention.html. Zugegriffen: 29. Juni 2016
38. Wendel U, Bettendorf M, Lindner M (2009) Neugeborenen-Screening in Deutschland. Positiver Screeningbefund - was ist zu tun? Schattauer, Stuttgart [u.a.]
39. Schmidtke J (Hrsg) (2007) Gendiagnostik in Deutschland. Status quo und Problemerkundung ; Supplement zum Gentechnologiebericht, 1. Aufl. Forschungsberichte der Interdisziplinären Arbeitsgruppen der Berlin-Brandenburgischen Akademie der Wissenschaften, Bd. 18. Forum W, Wiss. Verl, Limburg
40. Gemeinsamer Bundesausschuss (2015) Screening auf Mukoviszidose für Neugeborene beschlossen. https://www.g-ba.de/institution/presse/pressemitteilungen/585/. Zugegriffen: 29. Juni 2016
41. Gemeinsamer Bundesausschuss (2005) Kinder-Richtlinien (Neufassung Anlage 2: Neugeborenen-Screening und weitere Themen). https://www.g-ba.de/downloads/39-261-170/2004-12-21-Kinder-TMS.pdf. Zugegriffen: 28. Mai 2015
42. Gramer, G., Hoffmann, G.G., Nennstiel-Ratzel, U. (Hrsg) (2016) Das erweiterte Neugeborenenscreening – Erfolge und neue Herausforderungen. Geburtshilfe Frauenheilkd 76(05): 478. doi: 10.1055/s-0042-106914
43. Hildt E (Hrsg) (2009) Was bedeutet genetische Information?, [Online-Ausg.]. de Gruyter, Berlin [u.a.]
44. Kröger F (2010) Gentests beim Neugeborenen-Screening. http://www.gen-ethisches-netzwerk.de/gid/198/kroeger/gentests-beim-neugeborenen-screening. Zugegriffen: 05. Juli 2016
45. Genetic Alliance (2009) Understanding genetics. A New York, Mid-Atlantic guide for patients and health professionals. Genetic Alliance, Washington, DC
46. Rockman MV (2008) Reverse engineering the genotype-phenotype map with natural genetic variation. Nature 456(7223): 738–744. doi: 10.1038/nature07633
47. Department of Health (2015) The 100,000 Genomes Project. http://www.genomicsengland.co.uk/the-100000-genomes-project. Zugegriffen: 28. Mai 2015
48. Botkin JR, Belmont JW, Berg JS et al. (2015) Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. American journal of human genetics 97(1): 6–21. doi: 10.1016/j.ajhg.2015.05.022

Modul 3

Healthcare costs associated with breast cancer in Germany – a claims data analysis

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Healthcare costs associated with breast cancer in Germany: A claims data analysis

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Abstract

Purpose: This study estimates the healthcare costs associated with breast cancer (BC) for different treatment phases (initial, intermediate, terminal) in Germany from the payer's perspective.

Methods: The analysis uses claims data from the AOK Bayern covering 2011 to 2014 for continuously insured BC patients identified through inpatient and outpatient diagnoses. We calculate the healthcare costs attributable to BC using a control group design comparing the target population to a 1:2 matched control group adjusted for age, gender, comorbidities and mortality. For incident and prevalent BC cases, we calculate age-standardized phase-specific incremental costs stratified by cost domain.

Results: The initial, intermediate, and terminal phases comprise 3,954, 28,838, and 2,416 BC cases, respectively. With average costs of €21,386 in the first 11 months after diagnosis, the highest BC-related incremental healthcare costs can be found in the initial phase. In the intermediate phase, incremental costs totaled €2,866 per incident and €2,426 per prevalent case per year. In the remaining six months before death, the healthcare costs of incident and prevalent BC cases totaled €21,011 and €20,226, respectively; however, the incremental costs in the terminal phase totaled only €2,421 per incident and €1,557 per prevalent case. Healthcare costs decreased with age in most phases. The cost drivers depend on the treatment phase, with cytostatic drugs (and partly inpatient treatment) showing the highest economic impact in most phases.

Conclusion: The study concludes that BC care costs impose a relevant economic burden on statutory health insurance and vary substantially depending on the treatment phase.

Keywords: Breast cancer, disease cost, claims data, joinpoint, Germany

Introduction

Breast cancer (BC) is the world's second most common type of cancer and the most frequent in women. It represents 12% of all new cancer cases and 25% of all cancers in women [1]. In 2014, the age-standardized rate of incidence for women was 114.6 per 100,000 people in Germany, representing 69,220 new BC cases. Between 1980 and 2004, the incidence rate increased by about 50% [2]. Moreover, 559,900 German women (10-year prevalence) were living with a BC diagnosis in 2014, and 17,670 of them died from the disease. However, the relative five-year survival rate increased from 69% in 1980 to 81% in 2004 [3]. This improvement resulted from better treatment options (e.g., higher radiation doses [4]), new drug interventions [5], and earlier diagnoses (e.g., through mammography screening [6]).

The treatment and prognosis of BC are influenced by factors such as age, cancer stage, and tumor characteristics (status of estrogen receptor, progesterone receptor, human epidermal growth receptor 2, and the histologic grade) [7]. The disease stage (diseases stage 0-IV) influences disease-specific costs [8], which range from $60,637 (stage 0) to $134,682 (stage IV) per patient in the initial 12 months postdiagnosis. In the European Union, cancer incurred €126 billion of costs in 2009, €15 billion of which were attributable to BC. Accounting for 12% of total cancer costs, BC represents the second highest economic cancer burden [9]. Germany's costs of illness (COI) for BC were estimated at around 2,169 million euros in 2015 [10]. Germany has Europe's highest BC healthcare costs per person [9].

Cost analyses are important for political decision-making concerning prioritization and allocation [11]. Economic studies on BC cost patterns [12] include few analyses of BC-attributable health expenditures in Germany [13,14]. Only two studies have reported the COI of BC using claims data from a statutory health insurance (SHI) in Germany [14,15]. Claims data from SHIs are well suited for cost analyses since they are routinely collected for billing and reimbursement. However, a detailed analysis of overall direct disease-related costs that identifies the cost-driving factors is required because the extant studies differ substantially in their cost-calculation methods and cost domains considered. Moreover, unlike US data [16], the German data have not been analyzed for cost patterns through a clinically meaningful phase-of-care approach. Hence, this study estimates the BC-attributable health expenditures in Germany according to clinically relevant treatment phases.

Methods

Data source and study population

AOK Bayern provided data on all services reimbursed. Its sickness fund covered almost 4.3 million insured individuals in 2011 [17]. The analysis includes costs for inpatient and outpatient care, medication/cytostatic drugs, remedies and medical aids, rehabilitation, sick leave, and travel expenses. Patient identification was based on the ICD-10-GM system with ICD codes C50.0 to C50.9. Inclusion in the study population required documentation for at least one inpatient diagnosis or secured outpatient BC diagnosis in 2012. For exclusive identification by outpatient diagnosis, a second secured outpatient diagnosis was required within the following three quarters (i.e., occurring in 2013). We used 2011 to differentiate between incident and prevalent cases. Patients were defined as "incident" if no C50 diagnosis (outpatient/inpatient) was documented in 2011. All sample patients had to be continuously insured from 2011 to 2014 or until death (whichever came first). Male patients and patients under 18 were excluded, as both groups require special treatment.

Study design

We calculated BC-attributable costs using a control group design with pairwise matching. We compared BC patients to a 1:2 matched control group adjusted for gender, age, comorbidities, and mortality. The control sample consisted of randomly selected females continuously insured by AOK Bayern from 2011 to 2014 without a BC diagnosis. No replacement of control group members was allowed. Using the Elixhauser comorbidity score [18], we calculated comorbidities for both the intervention and control groups in 2011 on the basis of at least one inpatient/secured outpatient diagnosis. We were able to estimate BC costs in the terminal phase compared to a population with a similar mortality risk by matching BC cases who died during the observation period to controls that died in the same quarter. We used quarterly assignment to ensure the matching of deceased controls to each BC subject that died during the observation period. We ensured that all BC cases classified as "non-deceased" had not died within six months following the end of the observation.

Follow-up started for BC cases identified by hospitalization from the beginning of the month of the inpatient diagnosis. In German claims data, outpatient diagnoses are reported on a quarterly basis. Thus, within the quarter of each BC diagnosis, we defined the beginning of the month in which the first service date (according to the Uniform Valuation Scheme [EBM]) was documented as the approximate date of the index event. Follow-up ended in the latest two years following the index event or in the month of death, whichever came first. For controls, we considered follow-up periods

analogously to the BC cases. For matched pairs that did not die in the same month, we switched the controls' observation period to ensure that both observation periods were equal.

Following US studies [19–24,16,25], we divided the time after BC diagnosis into clinically relevant treatment phases: 1) initial phase, comprising the primary course of therapy (e.g., surgery, chemotherapy, radiation); 2) intermediate phase, including active surveillance and ongoing medication to prevent recurrence (e.g., hormone blockade) or treatment complications derived from the initial course of therapy; and 3) terminal phase, comprising (palliative) services provided in the last months before death. Lacking a scientific consensus on the duration of BC treatment phases, we first calculated the monthly BC-attributable costs and examined the average cost patterns from diagnosis to death. Using Trend Analysis Software from the National Cancer Institute [26], we applied joinpoint regression [22,27] to determine the length of each phase by assessing the points at which statistically significant changes occur in the cost slope.

As the observation period's maximum was two years and as BC cases showed different characteristics (e.g., incident vs. prevalent, alive vs. deceased), not all individuals were assigned to all phases of care. Following the literature [22,24], the observation period for BC cases who died was first assigned to the terminal phase of care. Any remaining time under observation, and all follow-up time for BC survivors, was then transferred to the initial treatment phase, and the most recent was assigned to the intermediate phase. In the initial and terminal phases, patients were excluded if they were not observable for the period determined by the joinpoint regression analysis. To be included in the intermediate phase, BC cases had to be observable for at least 12 months (costs are on an annual basis).

Calculation and presentation of healthcare costs

Copayments and out-of-pocket payments were not considered because costs were analyzed from the SHI perspective. Healthcare costs in euro were extracted from the database for both BC cases and controls. For each inpatient/rehabilitation stay and sick leave period, costs were divided by the length of stay/duration and calculated according to the start and end of each phase. Unfortunately, only annual outpatient care costs were available. To obtain monthly values, outpatient care costs were divided by the months under observation. To provide a better overview, the costs of cytostatic drugs and any remaining medication are reported separately. These medication costs include only prescriptions for outpatient care. The costs of drugs administered during inpatient episodes are part of total inpatient costs.

By comparing the cost differences between BC cases and controls, we could calculate the BC-attributable costs differentiated according to care phase. To adjust for age differences between SHIs , we standardized costs according to the five-year-age-structure of compulsory insured women in Germany for 2011 using data from the Federal Ministry of Health [17]. As the cases were few, we aggregated the costs of BC cases younger than 45 before standardization. Data management and statistical analyses were performed with SAS 9.4.

Results

Study population

The inclusion criteria produced 36,033 BC patients (see Figure 1). Of these, 32,707 were matched to 65,414 controls (1:2) and followed for a maximum of two years. After the matching, no significant differences were observed between BC cases and the controls concerning gender, age, comorbidity score, or mortality (see Table 1). Overall, 13% of BC cases were identified as incident, and 7% died within the follow-up period.

Through the joinpoint regression analysis, the initial treatment phase was defined as the month of diagnosis and the following 10 months. The terminal phase comprised the last six months of life, and the intermediate phase comprised all months between the initial and terminal phases. In the initial and terminal phase, the joinpoint regression analysis identified the points at which BC-related costs decreased significantly. Survivors included in one (92%) or two (8%) phases of care were followed for 23 months on average (SD = 1) and deceased individuals 14 months (SD = 5) on average.

Concerning demographic characteristics, Table 2 shows that age at phase onset averaged around 67 in the initial phase, 67 (incident cases) versus 68 years (prevalent cases) in the intermediate phase (with prevalent individuals being significantly older), and 78 (incident cases) versus 77 years (prevalent cases) in the terminal phase. The mean Elixhauser Score was 4 points for BC cases in the initial phase, 4 (incident cases) versus 6 (prevalent cases) points in the intermediate phase and was highest for individuals assigned to the terminal phase (7 versus 14 points). Within each phase, prevalent cases had a significantly higher comorbidity score than incident individuals ($p < 0.001$; Mann–Whitney-U-test).

Figure 1 Cohort selection

Table 1 Demographic characteristics after matching

Table 2 Baseline characteristics of the study population

Healthcare costs

The highest incremental BC costs are in the initial phase, followed by the terminal and intermediate phases. Tables 3 and 4 show the age-standardized healthcare costs in euro per cost component within each treatment phase for incident and prevalent patients.

As Table 3 shows, in the first 11 months following diagnosis, the average BC-related incremental costs totaled €21,386 per patient. At €11,239 per patient, cytostatic drugs represent more than half (53%) of initial phase costs, followed by inpatient care (23%), outpatient care (11%), and sick leave payments (8%). All remaining cost compounds are of minor importance.

In the intermediate phase, there were €2,866 mean BC-related incremental costs for incident and €2,426 for prevalent patients per year. For incident BC cases, almost a third of the costs is attributable to outpatient care. Cytostatic drugs, inpatient care, and sick leave payments each accounted for 15 to 20% of incremental BC-related costs. In contrast, accounting for over half of incremental costs in prevalent cases, the highest cost drivers are cytostatic drugs, followed by outpatient care (19%), inpatient care (12%), and remedies/medical aids (8%). In both incident and prevalent cases, all remaining medication, rehabilitation, and travel expenses have limited effects on incremental costs.

In the terminal phase (six months before death), BC costs totaled €21,011 in incident and €20,226 in prevalent cases; however, only €2,421 in incident cases and € 1,557 in prevalent cases were attributable to BC (compared to a control group with a similar mortality risk) because healthcare provision for control group members leads to significant costs. In the six remaining months before death, control group members' incremental inpatient costs of almost €3,200 are remarkably higher than those of BC cases. Moreover, negative incremental costs are also visible in rehabilitation services (incident/prevalent cases) and in sick leave payments and travel expenses (only in prevalent cases). In both incident and prevalent cases, the highest incremental cost drivers are, again, cytostatic drugs.

Several studies suggest that BC costs differ substantially by age [13,14]. Given the unstandardized costs stratified by five-year age groups (see appendix 1 and 2), incremental BC-related costs in the initial phase decreased substantially by age, with €54,273 in patients aged 25 to 29 compared to €4,367 in patients aged 85 or older. Though not apparent in all five-year age groups, this general trend is also evident in the intermediate and terminal phases.

Table 3 Age-standardized healthcare costs of incident BC cases in Germany

Table 4 Age-standardized healthcare costs of prevalent BC cases in Germany

Discussion

Cancer costs are typically first reported at the initial diagnosis, for a specific event like recurrence, or generally (for cancer survivors) in a specific year. However, costs may change over time when measured longitudinally starting from initial cancer diagnosis to long-term survival or death. In the US, phase-specific approaches are often used to analyze cancer cost patterns [16,25]. This study used claims data on real-life treatment to estimate the costs of BC care for Germany according to clinically relevant treatment phases. Using definitions of treatment phases according to joinpoint regression analysis, our study suggests that incremental BC-related costs differ substantially by care phase. Standardized BC-attributable costs were highest in the initial phase (11 months after diagnosis), averaging around €21,386 per person. Terminal care costs for the six remaining months before death totaled €2,421 in incident cases and €1,557 in prevalent cases. Costs of €2,866 for incident and €2,426 for prevalent cases were incurred each year in the intermediate phase. Calculated downward to six months, average costs in the intermediate phase are significantly lower ($p < 0.001$; Wilcoxon rank sum test) than for the terminal phase. Consistent with US BC studies, the costs follow a u-shaped curve, with costs highest near diagnosis and death, and lower in between. Comparing absolute costs with US data would be challenging due to differences in treatment structures and reimbursement schemes as well as methodological inconsistencies (e.g., in data sources, study populations, matching criteria, and phase selection methods).

European studies that have not applied a data-driven phase-of-care approach have also found that the economic burden of BC is highest in the periods following diagnosis and near death [13]. With standardized costs of €21,386 per person for the first 11 months after diagnosis, initial care costs in our study are much higher than are those in other studies. Damm et al. [15] reported on their conference poster based on German claims data that BC-attributable costs averaged around €4,278 per person in the first year after diagnosis. The 12-month costs of initial care have been reported to total around €8,553 for Sweden (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€) [28]) and €7,982 for Belgium [29]. However, studies differ in their data sources and cost calculation methods, as well as in the cost domains examined, leading to an underestimation of costs. Moreover, BC healthcare costs per case [30]/per person in the EU [9] are generally found to be more than two to three times higher in Germany than in Belgium or Sweden.

For the intermediate phase, annual direct BC-related healthcare costs were estimated at €2,866 for incident and €2,426 for prevalent cases. While Broekx et al. (2011) [29] reported much lower costs for the second year following diagnosis (€1,317 per patient for Belgium), our results are in line with Lidgren et al.'s (2007) [28] finding that annual direct costs for the second and following

years after initial BC diagnosis /recurrence totaled €2,359 (converted from SEK to € with an average 2005 exchange rate of 9.2822 SEK/€). Moreover, our results indicate that incident cases result in a significant ($p < 0.001$; Mann–Whitney-U-test) average cost impact of about €400 per year compared to prevalent cases. Given the proximity in time to the primary diagnosis, active surveillance and therapy for complications resulting from the initial course of therapy might be paramount. In prevalent cases, more than half of the costs are attributable to cytostatic drugs, indicating that our sample might include BC cases experiencing recurrent events. Although BC costs are generally higher near diagnosis and death, intermediate phase costs will become increasingly economically important, even if patients remain recurrence-free, as BC is showing increasing survival rates. Further examination of whether intermediate care costs will decline after initial diagnosis, as reported by Broekx et al. 2011 [29], is required.

Few studies have examined mortality costs. In the six-month terminal phase of care, direct BC-related healthcare costs averaged €2,421 in incident cases and €1,557 in prevalent cases. The only German study that calculated BC costs in the terminal phase found, by applying the propensity score method and adjusting for age and comorbidities, incremental direct healthcare costs of €10,833 in the last year before death [15]. However, unlike our analysis, this study did not compare deceased BC cases to controls that also died. The choice of comparison cohort can strongly impact the net costs of cancer [31], but the scientific literature displays no broad consensus on the choice of comparison group in cancer cost estimation. Matching exclusively on age and comorbidities might overestimate mortality costs, as not all the costs are a result of cancer. Contrariwise, comparing BC cases to a control group with a similar mortality risk leads to a high cost variance. Moreover, the length of the terminal phase was determined via joinpoint regression analysis, which identified the point at which costs decreased significantly. This may lead to the conclusion that, for BC cases that will lead to death in the foreseeable future, treatments such as inpatient episodes may be reduced and replaced by other forms of palliative care at home or in palliative care institutions. By contrast, the control group might include more individuals for whom death might have been unexpected and/or who require more intensive care. To derive BC-attributable mortality costs, we followed a conservative approach rather than cost overestimation.

Concerning direct costs, most studies report inpatient care [13,15,32] or both inpatient care and drugs [9] as the greatest cost drivers in BC. Our results suggest that the cost-driving factors depend on the care phase. In the initial and terminal phases, cytostatic drug costs were the main driver, whereas their impact in the intermediate phase was greater for prevalent than for incident patients. Inpatient care costs contributed to 23% of costs in the initial phase and 12 to 17% in the intermediate phase. The differences in the economic relevance of inpatient care and medication might reflect the fact that cytostatic drug costs represent only outpatient prescriptions and that

chemotherapy might also be administered during an inpatient episode and thus be included in inpatient costs.

Consistent with previous German studies [13,14], we found that direct BC-attributable costs decreased with age, particularly in the initial treatment phase (see appendix 1 and 2). Older women might have a lower chance of receiving aggressive treatment due to comorbidities or lower expected long-term benefits, or because they reject chemotherapy. Similar to Gruber et al. (2009) [14], we found that, while 97% of healthcare costs were BC-attributable in 25 to 29-year-old women, the share decreased to 54% in women over 85. In the intermediate phase, the share decreased from 77% to 24% in incident and from 71% to 15% in prevalent cases. Younger women might be more likely to take time off from work after diagnosis and, as they receive more aggressive treatment, may also experience more lasting effects from the initial therapy. Hence, if BC could be detected earlier or even prevented, especially among young women, the overall cost burden could be reduced.

This study is limited by the nature of its data source. First, as claims data are routinely collected for billing and reimbursement, they do not include information on clinical parameters, thus preventing cost stratification by cancer stage or tumor type. However, we differentiated between incident and prevalent patients. Second, claims data lack information on cause of death. Hence, BC cases assigned to the terminal phase might have died from causes other than BC. Third, as only annual (calendar year) outpatient care cost data were available, monthly costs might not have been assigned adequately to the care phases. However, in the 12-month intermediate phase, more than 80% of the individuals started their phase in the first quarter of 2012, covering almost the full calendar year. Fourth, we used data from one regional sickness fund. As health insurances differ (e.g., in terms of age, gender and social status [33,34], our results' generalizability might be limited. The median age at diagnosis and death was about three and five years, respectively, above the median age reported in registry data [3], because the AOK Bayern included a higher proportion of insured women 70 or older and a lower proportion of insured women 30 to 70 relative to all statutory insured women in Germany in 2011 [17]. To address this issue and generalize costs, we standardized them according to gender and the five-year age structure of the German health insurance population. We thus calculated BC-related incremental costs under real-life conditions, including all cost domains that might be relevant from the SHI perspective. Ours is the first study to calculate direct BC costs for Germany using an incidence-based phase-of-care approach.

Conclusion

The economic burden of BC represents a major challenge for the SHI. This study indicates that BC healthcare costs depend on treatment phase, with higher costs near diagnosis and death and lower costs in between. The greatest economic burden occurs in the first 11 months following diagnosis and depends heavily on patient age, with cytostatic drugs and inpatient care accounting for three quarters of total costs. Comparing deceased BC patients to deceased controls shows comparatively low costs in the terminal phase, as BC treatment might be replaced by other forms of care if death is foreseeable. Although intermediate phase costs are lower than those in phases near diagnosis and death, they remain substantial. Future studies should stratify German BC care costs according to cancer stage and tumor characteristic by linking claims data with clinical information.

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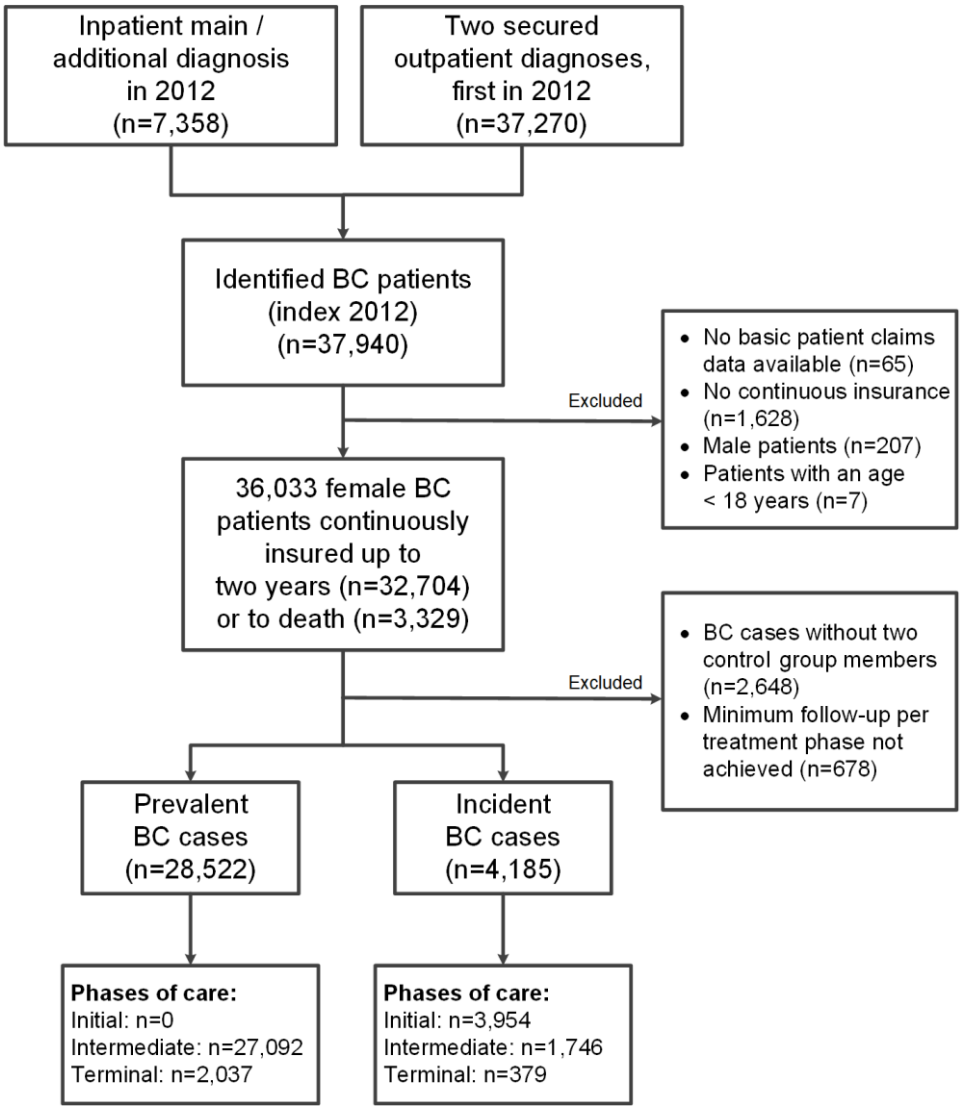

Figure 1 Cohort selection

Table 1 Demographic characteristics after matching

	Gender: female		Age		Elixhauser Comorbidity Score		Mortality		n
	%	p[1]	Mean [SD]	p[2]	Mean [SD]	p[2]	%	p[1]	
BC cases	100	1	67.32 [12.23]	0.796	6.10 [8.81]	0.999	7.39	1	32707
Controls	100		67.33 [12.23]		6.10 [8.81]		7.39		65414

[1] Chi²-Test; [2]U-test following Mann & Whitney; SD = standard deviation

Table 2 Baseline characteristics of BC cases

	Age (at phase onset)				Elixhauser Comorbidity Score				
Phase	Mean [SD]	Median	Min	Max	Mean [SD]	Median	Min	Max	n
Initial									
Incident	67.07 [13.26]	69	21	101	4.05 [7.34]	1	-11	49	3954
Intermediate									
Incident	67.03 [13.12]	69	21	102	3.84 [7.29]	0	-10	49	1746
Prevalent	67.98 [11.89]	70	19	107	5.95 [8.67]	3	-14	58	27092
Terminal									
Incident	77.90 [12.59]	80	32	101	7.43 [8.66]	6	-7	46	379
Prevalent	77.14 [11.80]	79	25	103	13.87 [10.52]	13	-7	52	2037

SD = standard deviation

Table 3 Age-standardized healthcare costs of incident BC cases in Germany (in €, mean [standard deviation])

	Initial phase (11 months)			Intermediate phase (12 months)			Terminal phase (6 months)		
Cost sector	**BC cases**	**controls**	**Increment**	**BC cases**	**controls**	**Increment**	**BC cases**	**controls**	**Increment**
Medication	12070 [24036]	525 [1868]	**11545** [24176]	1186 [7070]	491 [1516]	**695** [7237]	4770 [10743]	1365 [3551]	**3405** [11151]
Cytostatic drugs	11247 [23616]	8 [270]	**11239** [23618]	577 [6769]	0 -	**577** [6769]	3441 [10138]	333 [1671]	**3108** [10208]
Other medication	823 [2007]	517 [1833]	**306** [2713]	609 [1848]	491 [1516]	**118** [2383]	1329 [2805]	1032 [2854]	**297** [4003]
Remedies/medical aids	526 [1083]	257 [922]	**269** [1412]	573 [1144]	289 [767]	**284** [1368]	909 [1359]	439 [712]	**470** [1577]
Outpatient care	3131 [2549]	773 [624]	**2358** [2633]	1736 [1620]	835 [623]	**901** [1750]	2178 [2132]	902 [1173]	**1276** [2314]
Inpatient care	6279 [7286]	1338 [5627]	**4941** [9097]	1864 [4515]	1383 [4493]	**481** [6376]	11534 [10048]	14708 [24584]	**-3174** [26035]
Rehabilitation	182 [755]	87 [564]	**95** [904]	118 [627]	94 [578]	**24** [850]	134 [712]	226 [954]	**-92** [1197]
Sick leave payments	1868 [4425]	129 [1054]	**1739** [4486]	560 [2094]	111 [885]	**449** [2224]	770 [1965]	282 [1341]	**488** [2342]
Travel expenses	514 [860]	75 [370]	**439** [935]	112 [392]	80 [398]	**32** [555]	716 [911]	668 [989]	**48** [1328]
Sum	24570 [29515]	3184 [7206]	**21386** [30523]	6149 [10186]	3283 [5885]	**2866** [11821]	21011 [15817]	18590 [25569]	**2421** [28708]

Table 4 Age-standardized healthcare costs of prevalent BC cases in Germany (in €, mean [standard deviation])

	Intermediate phase (12 months)			Terminal phase (6 months)		
Cost sector	**BC cases**	**controls**	**Increment**	**BC cases**	**controls**	**Increment**
Medication	1983 [10367]	592 [1748]	**1391** [10463]	5477 [11572]	1506 [3464]	**3971** [11903]
Cytostatic drugs	1295 [9877]	13 [367]	**1282** [9875]	4101 [11305]	393 [2024]	**3708** [11329]
Other medication	688 [1900]	579 [1691]	**109** [2504]	1376 [2160]	1113 [2572]	**263** [3370]
Remedies/medical aids	518 [906]	318 [889]	**200** [1237]	905 [1420]	701 [1276]	**204** [1850]
Outpatient care	1314 [1222]	864 [702]	**450** [1391]	1694 [1569]	921 [1126]	**773** [1887]
Inpatient care	1745 [4667]	1458 [4108]	**287** [6096]	11269 [11716]	14434 [23972]	**-3165** [26329]
Rehabilitation	96 [474]	95 [471]	**1** [657]	112 [794]	174 [917]	**-62** [1203]
Sick leave payments	216 [1176]	143 [945]	**73** [1491]	161 [1029]	202 [1269]	**-41** [1644]
Travel expenses	109 [373]	85 [358]	**24** [503]	608 [784]	731 [1181]	**-123** [1418]
Sum	5981 [12878]	3555 [5809]	**2426** [13804]	20226 [17885]	18669 [24962]	**1557** [30080]

Appendix 1: Unstandardized healthcare costs of incident BC cases (n) in Germany by age group (in €, mean [standard deviation])

Age	Initial phase (11 months)				Intermediate phase (12 months)				Terminal phase (6 months)			
	n[1]	BC cases	controls	Increment	n[1]	BC cases	controls	Increment	n[1]	BC cases	controls	Increment
< 20												
20-24	6	12380 [27084]	2270 [4780]	**10110** [22875]	2	1645 [1930]	687 [454]	**959** [1247]				
25-29	13	55784 [48537]	1512 [2256]	**54273** [46892]	8	8765 [8657]	1995 [2234]	**6769** [9236]				
30-34	28	55666 [54128]	4631 [17069]	**51035** [57448]	15	6201 [5657]	1245 [1308]	**4956** [5974]	3	21472 [8933]	33350 [32651]	**-11878** [36109]
35-39	58	47073 [34753]	2226 [5406]	**44848** [35353]	24	8030 [6232]	2209 [3773]	**5821** [7011]	1	36536 -	47152 [31664]	**-10616** [31664]
40-44	127	43444 [39450]	2503 [4698]	**40941** [39569]	61	6316 [10138]	2643 [4713]	**3673** [11046]	5	32523 [12181]	15188 [16580]	**17336** [18743]
45-49	265	36928 [34406]	2359 [4461]	**34568** [34395]	127	6641 [7734]	2489 [5257]	**4152** [9183]	7	25670 [13349]	16836 [15456]	**8834** [14423]
50-54	351	32289 [32679]	2610 [5777]	**29679** [33274]	162	7381 [14994]	2604 [4790]	**4776** [15764]	14	21192 [11439]	19198 [20324]	**1994** [24224]
55-59	372	29875 [33338]	3257 [6366]	**26618** [34017]	168	5262 [7208]	2518 [3930]	**2745** [8262]	16	28432 [18467]	26725 [38543]	**1707** [41718]
60-64	488	23604 [28450]	2657 [4284]	**20948** [28806]	231	6592 [16187]	3007 [5452]	**3585** [17147]	22	21935 [20345]	21119 [33574]	**816** [39990]
65-69	454	18715 [21239]	3573 [9634]	**15142** [23150]	209	4976 [8811]	3697 [6977]	**1279** [11345]	20	23165 [15546]	21126 [25386]	**2039** [29010]
70-74	619	17577 [18936]	3311 [9113]	**14266** [20590]	266	5990 [9313]	3528 [5936]	**2461** [11070]	52	22154 [20335]	17373 [31987]	**4782** [38001]
75-79	542	13252 [13016]	4352 [10881]	**8900** [16796]	233	5494 [7853]	3798 [5826]	**1695** [9758]	59	13788 [10919]	16682 [20931]	**-2894** [24490]
80-84	354	10673 [9807]	3768 [6056]	**6905** [11138]	150	6686 [9263]	5426 [9763]	**1260** [13807]	67	10658 [9745]	10036 [12235]	**622** [13846]
> 84	277	8141 [9159]	3774 [4785]	**4367** [10546]	90	5590 [5758]	4248 [5023]	**1342** [7409]	113	7316 [6981]	7514 [6868]	**-197** [9729]

[1] number of BC cases

Appendix 2: Unstandardized healthcare costs of prevalent BC cases (n) in Germany by age group (in €, mean [standard deviation])

Age	Intermediate phase (12 months)				Terminal phase (6 months)			
	n[1]	BC cases	controls	Increment	n[1]	BC cases	controls	Increment
< 20	1	2815 -	2093 [1592]	**722** [1592]				
20-24	7	9269 [15984]	1592 [1311]	**7677** [14712]	1	34596 -	129052 [139238]	**-94456** [139238]
25-29	28	6941 [13800]	2040 [3346]	**4901** [14559]	1	14984 -	16177 [1911]	**-1193** [1911]
30-34	91	12884 [24285]	2654 [3935]	**10231** [24406]	1	41846 -	22473 [2541]	**19373** [2541]
35-39	199	9607 [22449]	2722 [5456]	**6884** [23202]	4	34836 [26342]	23955 [16940]	**10881** [37205]
40-44	668	7980 [20220]	3015 [5831]	**4965** [20514]	15	24593 [20194]	14533 [13732]	**10060** [24558]
45-49	1303	6873 [19118]	2858 [6005]	**4015** [19922]	40	20982 [10612]	23881 [25352]	**-2899** [25536]
50-54	2265	5729 [11599]	3232 [6216]	**2496** [12596]	59	30267 [27052]	19504 [19029]	**10763** [35343]
55-59	2710	5456 [12449]	3423 [5758]	**2033** [13085]	88	26563 [22577]	23413 [30375]	**3151** [39044]
60-64	3334	5216 [10754]	3234 [6304]	**1982** [12103]	144	20037 [12060]	21037 [28764]	**-1000** [31245]
65-69	3651	5618 [11376]	3519 [5794]	**2099** [12155]	174	20769 [17320]	21903 [29952]	**-1134** [34613]
70-74	5293	5532 [9235]	3835 [5859]	**1697** [10555]	294	16368 [12549]	17391 [20177]	**-1024** [23794]
75-79	3718	5826 [9067]	4229 [5823]	**1597** [10491]	330	15569 [13381]	13656 [14843]	**1914** [20287]
80-84	2287	5452 [6523]	4458 [5320]	**994** [8194]	364	11314 [10095]	11714 [15814]	**-400** [18775]
> 84	1537	5087 [5298]	4333 [4826]	**754** [6991]	522	7633 [6909]	7533 [7266]	**100** [9652]

[1] number of BC cases

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN. Int J Cancer 136: E359–86.

2. Kaatsch P, Spix C, Katalinic A, Hentschel S, Luttmann S, Stegmaier C, Caspritz S, Christ M, Ernst A, Folkerts J, Hansmann J, Klein S, Kranzhöfer K, Kunz B, Manegold K, Penzkofer A, Treml K, Weg-Remers S, Wittenberg K, Baras N, Barnes B, Bertz J, Buttmann-Schweiger N, Dahm S, Fiebig J, Franke M, Haberland J, Kraywinkel K, Wienecke A, Wolf U (2015) Contributions on federal health monitoring: cancer in Germany 2011/2012 [German]. Berlin: Robert Koch-Institut. [Gesundheitsberichterstattung für Deutschland].

3. Robert Koch-Institut (2017) Cancer in Germany 2013/2014 [German]: RKI-Bib1 (Robert Koch-Institut).

4. Bartelink H, Horiot J-C, Poortmans PM, Struikmans H, van den Bogaert W, Fourquet A, Jager JJ, Hoogenraad WJ, Oei SB, Wárlám-Rodenhuis CC, Pierart M, Collette L (2007) Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 25: 3259–3265.

5. Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A (2017) Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ (Clinical research ed.), 359: j4530.

6. Kaplan HG, Malmgren JA, Atwood MK, Calip GS (2015) Effect of treatment and mammography detection on breast cancer survival over time: 1990–2007. Cancer 121: 2553–2561.

7. Hamm C, El-Masri M, Poliquin G, Poliquin V, Mathews J, Kanjeekal S, Alam Y, Kulkarni S, Elfiki T (2011) A single-centre chart review exploring the adjusted association between breast cancer phenotype and prognosis. Curr Oncol 18: 191–196.

8. Blumen H, Fitch K, Polkus V (2106) Comparison of treatment costs for breast cancer, by tumor stage and type of service. American Health & Drug Benefits 9: 23–32.

9. Luengo-Fernandez R, Leal J, Gray A, Sullivan R (2013) Economic burden of cancer across the European Union: A population-based cost analysis. Lancet Oncol 14: 1165–1174.

10. Cost of illness: Germany, Years, Disease diagnoses (ICD-10) (2015) [https://www-genesis.destatis.de/genesis/online/logon?sequenz=tabelleErgebnis&selectionname=23631-0001&sachmerkmal=ICD10Y&sachschluessel=ICD10-C00-C97,ICD10-C00-C14,ICD10-C15-C26,ICD10-C16,ICD10-C18,ICD10-C20,ICD10-C25,ICD10-C30-C39,ICD10-C33-C34,ICD10C43-C44,ICD10-C50,ICD10-C51-C58,ICD10-C53,ICD10-C60-C63,ICD10-C61,ICD10-C64-C68,ICD10-C67,ICD10-C81-C96,ICD10-C91-C95,].

11. Stollenwerk B, Welchowski T, Vogl M, Stock S (2106) Cost-of-illness studies based on massive data: a prevalence-based, top-down regression approach. Eur J Health Econ 17: 235–244.

12. Radice D, Redaelli A (2003) Breast cancer management: quality-of-life and cost considerations. PharmacoEconomics 21: 383–396.

13. Damm O, Hodek J-M, Greiner W (2009) Methodological standards for cost-of-illness studies using breast cancer, prostate cancer and colon cancer as an example [German]. Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen 103: 305–316.

14. Gruber EV, Stock S, Stollenwerk B (2012) Breast cancer attributable costs in Germany: a top-down approach based on sickness funds data. PloS One, 7: e51312.

15. Damm O, Leppert F, Greiner W (2012) PCN47 Cost-of-Illness of common cancer types - results of a health insurance claims data analysis. Value Health 15: A417.

16. Yabroff KR, Lund J, Kepka D, Mariotto A (2011) Economic burden of cancer in the United States: estimates, projections, and future research. Cancer Epidem Biomar 20: 2006–2014.

17. Member statistics KM6 (Statutory health insurance: Insured persons) (2018) [https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Statistiken/GKV/Mitglieder_Versicherte/KM6_2011.xls].

18. Van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ (2009) A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Medical care, 47: 626–633.

19. Riley GF, Potosky AL, Lubitz JD, Kessler LG (1995) Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. Med Care 33: 828–841.

20. Taplin SH, Barlow W, Urban N, Mandelson MT, Timlin DJ, Ichikawa L, Nefcy P (1995) Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. J Natl Cancer 87: 417–426

21. Fireman BH, Quesenberry CP, Somkin CP, Jacobson AS, Baer D, West D, Potosky AL, Brown ML (1997) Cost of care for cancer in a health maintenance organization. Health Care Financ R 18: 51–76.

22. Brown ML, Riley GF, Schussler N, Etzioni R (2002) Estimating health care costs related to cancer treatment from SEER-Medicare data. Med Care 40: IV-104-17.

23. Warren JL, Brown ML, Fay MP, Schussler N, Potosky AL, Riley GF (2002) Costs of treatment for elderly women with early-stage breast cancer in fee-for-service settings. J Clin Oncol 20: 307–316

24. Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, Brown ML (2008) Cost of care for elderly cancer patients in the United States. J Natl Cancer I 100: 630–641.

25. Barlow WE (2009) Overview of methods to estimate the medical costs of cancer. Med Care 47: S33-6.

26. Joinpoint Regression Program, Version 4.6.0.0 (April 16, 2018) Statistical methodology and applications branch, Surveillance Research Program [https://surveillance.cancer.gov/joinpoint/]

27. Kim HJ, Fay MP, Feuer EJ, Midthune DN (2000) Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 19: 335–351.

28. Lidgren M, Wilking N, Jönsson B, Rehnberg C (2007) Resource use and costs associated with different states of breast cancer. Int J Technol Assess 23: 223–231.

29. Broekx S, Den Hond E, Torfs R, Remacle A, Mertens R, D'Hooghe T, Neven P, Christiaens M-R, Simoens S (2011) The costs of breast cancer prior to and following diagnosis. Eur J Health Econ 12: 311–317.

30. A review of breast cancer care and outcomes in 18 countries in Europe, Asia, and Latin America (2009) [http://www.comparatorreports.se/A_review_of_breast_cancer_care_and_outcomes_26Oct2009.pdf].

31. Chen AB, Li L, Cronin AM, Brooks GA, Kavanagh BD, Schrag D (2017) Estimating costs of care attributable to cancer: does the choice of comparison group matter? Health services research.

32. Wai ES, Trevisan CH, Taylor SCM, Mates D, Jackson JS, Olivotto IA (2001) Health system costs of metastatic breast cancer. Breast Cancer Res Tr 65: 233–240.

33. Hoffmann F, Icks A (2012) Structural differences between health insurance funds and their impact on health services research: results from the Bertelsmann Health-Care Monitor [German]. Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)) 74: 291–297.

34. Jaunzeme J, Eberhard S, Geyer S (2013) How “representative” are SHI (statutory health insurance) data? Demographic and social differences and similarities between an SHI-insured population, the population of Lower Saxony, and that of the Federal Republic of Germany using the example of the AOK in Lower Saxony [German]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 56:

Modul 4

Individualisierte Medizin bei ausgewählten Krebserkrankungen

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Individualisierte Medizin bei ausgewählten Krebserkrankungen /

Individualized medicine in selected oncological diseases

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Keywords: breast cancer; individualized medicine; lung cancer; oncology; personalized medicine.

Keywords: Brustkrebs; Individualisierte Medizin; Lungenkrebs; Onkologie; personalisierte Medizin.

Zusammenfassung

Durch zielgerichtete Therapien (TT) wurden bereits in einigen onkologischen Indikationen Verbesserungen in der Behandlung erzielt. Für Lungenkrebs sind bisher 5 und für Brustkrebs 11 Substanzen zur TT zugelassen. Somit konnten beispielsweise Erhöhungen der Überlebenszeit und ein verbessertes Therapieansprechen bei EGFR-positiven Lungenkrebs-Patienten oder auch Verbesserungen der Lebensqualität bei Brustkrebspatienten nachgewiesen werden. Einem breiten Einsatz von TT stehen jedoch aktuell einige medizinische und ökonomische Herausforderungen entgegen.

Abstract

The administration of targeted therapies (TT) has improved the treatment of some oncological indications. 5 substances for TT in lung cancer and 11 substances for TT in breast cancer have been approved so far. An increased survival time and better response to treatment in EGFR-positive lung cancer patients as well as an increased quality of life in breast cancer could be proven. Actually, some economic and medical challenges preclude a wider application of targeted therapies in the oncology.

Patienten lassen sich neben anamnetischen (persönlichen Daten, Lebensgewohnheiten etc.) und krankheitsbezogenen Daten (z.B. Verdachts-, Haupt-, und Nebendiagnosen)

auch zunehmend durch genetische Daten unterscheiden. Sowohl die Entstehung von Krankheiten als auch das Therapieansprechen sind ein multifaktorielles Zusammenspiel. Fortschritte in der humangenetischen Forschung ermöglichen ein wachsendes Verständnis über den Einfluss von genetischen Faktoren. Genomweite Assoziationsstudien sind dabei ein wesentliches Instrument für die Identifikation von Phänotyp-Genotyp-Korrelationen [1]. Dieses genetische Wissen ist der Grundstein für die individualisierte bzw. personalisierte Medizin (PM). Obwohl beide Begriffe in der Literatur häufig synonym verwendet werden, lassen sie sich grundsätzlich voneinander abgrenzen. Therapeutische Unikate, z.B. individualisierte Zelltherapien, werden anhand des Genprofils eines Patienten maßgeschneidert ([2]. PM zielt hingegen auf die Stratifizierung des Patientenkollektives, u.a. mittels Biomarkern oder Genmutationen, in Subgruppen ab [3]. Biomarker sind mess- und evaluierbare objektive Eigenschaften, die sowohl als Indikator für normale biologische und pathogene Prozesse als auch für pharmakologische Reaktionen auf therapeutische Interventionen eingesetzt werden können [4]. Biomarkertestungen gehören im Gegensatz zu den therapeutischen Unikaten bereits zur medizinischen Versorgung und können zu prädiktiven, diagnostischen und prognostischen Zwecken eingesetzt werden (Abb 1).

Abbildung 1. Klassifizierung von Biomarkern

Prädiktiv
- Wahrscheinlichkeit eine spezifische Krankheit zu entwickeln
- Wahrscheinlichkeit des Therapieansprechens bzw. Entwicklung von unerwünschten Nebenwirkungen

Beispiele:
- EGFR –Mutation bei NSCLC oder KRAS – Mutation bei Darmkrebs: Information über die Ansprechrate zielgerichteter Therapien
- Mutationen BRCA I und BRCA II: Information über das Risiko Brustkrebs zu entwickeln

Prognostisch
- Aussage über den potentiellen Krankheitsverlauf (z.B. Rezidivrisiko)
- Aussage über die voraussichtlichen Heilungschancen

Beispiele:
- HER2-positiv oder negativ: Information über die Aggressivität des Mammakarzinoms (kann ebenfalls prädiktive Informationen zum Therapieansprechen liefern)

Diagnostisch
- Identifikation, Klassifikation oder Früherkennung einer Erkrankung

Beispiel:
- PSA-Wert kann auf ein Prostatakarzinom hinweisen

Abkürzungen: EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; KRAS: Kirsten rat sarcoma; HER2: Human epidermal growth factor receptor vom Typ 2; BRCA: Breast cancer; PSA: Prostata spezifisches Antigen

Hohe Behandlungskosten und unzureichende therapeutische Outcomes sind kennzeichnend für einige onkologische Indikationen. Vor allem in Hinblick auf die Prävalenz- und Sterblichkeitsrate wird die Relevanz des Themas deutlich. Krebserkrankungen sind in Deutschland die zweithäufigste Todesursache [5] und es wird geschätzt, dass im Jahr 2012 in Deutschland 252.060 Männer und 225.890 Frauen neu an Krebs erkrankten [6]. Ebenso wie jeder Patient, ist auch jede Krebserkrankung individuell. An diese Individualität knüpfen zielgerichtete Therapien, sogenannte „targeted therapies“ (TT), an. Neben der Vermeidung von Nebenwirkungen und der damit einhergehenden Erhöhung der Patientensicherheit, zielen stratifizierte Therapien vor allem auch auf die Verbesserung der Outcomes (Überlebenszeit, Lebensqualität etc.) ab. TT blockieren bei Tumorerkrankungen spezifische Moleküle, die einen Einfluss auf das Wachstum und die Ausbreitung der Erkrankung haben [7].

Das Lungenkarzinom ist bei Männern die häufigste Krebstodesursache [6] und in 85% - 90% der Erkrankungen handelt es sich um das nicht-kleinzellige Lungenkarzinom (NSCLC) [9]. Spezifische Biomarker bzw. Onkogene wurden bei über 50% der NSCLC-Patienten identifiziert, wobei EGFR, KRAS und ALK am häufigsten festgestellt wurden (Sequist et al., 2011). In dieser Indikation sind bisher fünf Wirkstoffe (Tab 1) zur PM zugelassen. Durch TT konnten in der Behandlung von Lungenkrebs deutliche Fortschritte erzielt werden. Bei EGFR-positiven Patienten konnte bspw. im Vergleich zur alleinigen Chemotherapie durch die Verabreichung eines der zugelassenen Wirkstoffe sowohl eine längere progressionsfreie Überlebenszeit als auch ein besseres Therapieansprechen erzielt werden [11-14].

Beim Mammakarzinom, der häufigsten Krebstodesursache bei Frauen (RKI und GEKID, 2015), konnten ebenfalls eine Vielzahl von Biomarkern identifiziert werden. Die primäre Stratifizierung wird in dieser Indikation u.a. anhand der Hormonrezeptoren Östrogen und Progesteron und des Rezeptors Her2 vollzogen [15]. Bisher wurden 11 Substanzen zur personalisierten Therapie von Brustkrebs zugelassenen (Tab 1). Durch die Verabreichung von TT konnte u.a. eine Erhöhung der Gesamtüberlebensrate, des progressionsfreien Überlebens und/oder eine Verbesserung der Lebensqualität von Brustkrebspatienten erzielt werden [16-18].

Tabelle 1. In den Indikationen Brust- und Lungenkrebs zugelassene personalisierte Medikamente [10]

Wirkstoff	Krankheitsgebiet	Test auf	Testbeschreibung	Wirkstoffanwendung
Afatinib*	Lungenkrebs	Wirksamkeit	Test auf EGFR- Mutation	Verabreichung des Wirkstoffes nur bei EGFR-positiven Patienten
Erlotinib***	Lungenkrebs	Wirksamkeit		
Gefitinib*	Lungenkrebs	Wirksamkeit		
Crizotinib*	Lungenkrebs	Wirksamkeit	Test auf EML4-ALK - Protein	Verabreichung des Wirkstoffes nur bei positivem Testergebnis
Ceritinib*	Lungenkrebs	Wirksamkeit	Test auf Anaplastische-Lymphomkinase (ALK)	Verabreichung des Wirkstoffes nur bei positivem Testergebnis
Anastrozol**	Brustkrebs	Wirksamkeit	Test auf Hormonrezeptor-positive Brustkrebszellen (positive = (normale) Expression von Estrogen – und (/oder) Progesteron-Rezeptoren)	Verabreichung des Wirkstoffes nur bei positivem Testergebnis
Fulvestrant*	Brustkrebs	Wirksamkeit		
Letrozol**	Brustkrebs	Wirksamkeit		
Tamoxifen	Brustkrebs	Wirksamkeit		
Toremifen*	Brustkrebs	Wirksamkeit		
Trastuzumab*	Brustkrebs und Magenkrebs	Wirksamkeit	Test auf HER2 –Überexpression	Verabreichung des Wirkstoffs nur bei nachgewiesener Überexpression
Trastuzumab emtansin*	Brustkrebs	Wirksamkeit		
Pertuzumab*	Brustkrebs	Wirksamkeit		
Lapatinib*	Brustkrebs	Wirksamkeit		
Exemestan**	Brustkrebs	Wirksamkeit	Test auf Estrogenrezeptor-positive Brustkrebszellen (positiv = Expression von Estrogen-Rezeptoren nachweisbar)	Verabreichung des Wirkstoffes nur bei positivem Testergebnis
Everolimus*	Brustkrebs	Wirksamkeit	Test auf HER2/Neu-Expression	Verabreichung des Wirkstoffes nur bei HER2/neu-negativen Tumoren

* Für diese Wirkstoffe ist ein vorheriger Pflichttest vorgeschrieben
** Für diese Wirkstoffe ist ein Pflichttest vorgeschrieben; jedoch bei metastasierenden Brustkrebs ist der Wirkstoff auch ohne vorherigen Test anwendbar
*** Anwendung als Erhaltungstherapie, Zweit- und Folgelinienbehandlung erfolgt unabhängig vom Mutationsstatus

Aktuell sind insgesamt 45 Wirkstoffe zur PM in Deutschland zugelassen. Ein Großteil davon wird im onkologischen Setting angewendet. Der Einsatz ist jedoch auf wenige Indikationen (u.a. Brustkrebs, Lungenkrebs, Melanom, Leukämie, Darmkrebs) begrenzt [15]. Inwieweit die Personalisierung in der Onkologie voranschreitet, kann zum aktuellen

Zeitpunkt nicht abschließend beurteilt werden. Eine breite Anwendung von PM bedarf einer Ausweitung der onkologischen Indikationsgebiete für TT. In vielen Indikationen wurden ähnliche Ansatzsatzpunkte für TT (bspw. EGFR) identifiziert. Somit sind zukünftig vermehrt indikationsübergreifende Anwendungen denkbar. Grundvoraussetzung für einen breiten Einsatz ist die Identifikation weiterer biologischer Zusammenhänge und verlässlicher Biomarker. Da das Therapieansprechen ein multifaktorielles Zusammenspiel ist, sind die Effekte von TT jedoch nie eindeutig vorauszusagen. Die Anwendung einer TT kann bspw. in einer anderen Indikation, trotz des identifizierten gleichen Onkogens, wirkungslos sein. Die enge Verzahnung von Diagnostik und Therapie erfordert eine verbesserte Validierung und Qualitätssicherung genetischer Tests. Eine effektive Selektion hat einen Einfluss auf das Kosten-Nutzenverhältnis: unnötige Therapien oder das Ausbleiben wirksamer Behandlungen werden verhindert. Zudem sollten in Zukunft in der Evidenzbewertung die Spezifika von PM (kleine Patientengruppen) größere Berücksichtigung finden. Solang, aufgrund der relativ hohen Kosten, erhebliche Zweifel an der Kosteneffektivität von TT bestehen, sind die Kostenträger restriktiv in der Erstattung. Die Entwicklung von Kostenstrukturen und der Testgüte sind u.a. Faktoren die hierauf einen entscheidenden Einfluss haben werden.

Die genannten Aspekte verdeutlichen die Notwendigkeit weiterer medizinischer und ökonomischer Forschung, um eine breite Anwendungsbasis für PM zu schaffen.

Interessenkonflikt: Die korrespondierende Autorin erklärt, dass kein Interessenkonflikt besteht.

Korrespondenzanschrift

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Literatur

1. van der Sluis S, Posthuma D, Dolan CV. TATES: efficient multivariate genotype-phenotype analysis for genome-wide association studies. PLoS genetics 2013;9(1):e1003235.
2. Deutscher Bundestag (Hrsg). Bericht des Ausschusses für Bildung, Forschung und Technikfolgenabschätzung (18. Ausschuss) gemäß § 56a der Geschäftsordnung: Drucksache 16/12000; 2009.
3. Diamandis M, White, Nicole M A, Yousef GM. Personalized medicine: marking a new epoch in cancer patient management. Molecular cancer research MCR 2010;8(9):1175–87.
4. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical pharmacology and therapeutics 2001;69(3):89–95.
5. Statistisches Bundesamt (Hrsg.). Anzahl der Gestorbenen nach Kapiteln der ICD-10 2016; https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Gesundheit/Todesursachen/Tabellen/GestorbeneAnzahl.html.
6. Robert Koch-Institut (RKI) (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID) (Hrsg). Krebs in Deutschland 2011/2012. 2015. http://www.gekid.de/Doc/krebs_in_deutschland_2015.pdf
7. Krebsinformationsdienst (KID) Deutsches Krebsforschungszentrum (Hrsg). Zielgerichtete Krebstherapien: Targeted Therapies, 2012, https://www.krebsinformationsdienst.de/behandlung/moderne-krebstherapien.php
8. American Cancer Society. What ist non-small cell lung cancer? 2015, http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf
9. Sequist LV, Heist RS, Shaw AT, Fidias P, Rosovsky R, Temel JS, et al. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. Annals of oncology official journal of the European Society for Medical Oncology / ESMO 2011;22(12):2616–24.
10. Verband forschender Pharmaunternehmen (VfA) (Hrsg.). In Deutschland zugelassene Arzneimittel für die personalisierte Medizin; 2015, http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/individualisierte-medizin.html
11. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. The New England journal of medicine 2010;362(25):2380–8.
12. Mok TS, Wu Y, Thongprasert S, Yang C, Chu D, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. The New England journal of medicine 2009;361(10):947–57.
13. Schuler M, Yang JC, Park K, Kim J, Bennouna J, Chen Y, et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. Ann Oncol 2016;27:417-23.
14. Shaw AT, Kim D, Nakagawa K, Seto T, Crinó L, Ahn M, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. The New England journal of medicine 2013;368(25):2385–94.
15. Parise CA, Caggiano V. Breast Cancer Survival Defined by the ER/PR/HER2 Subtypes and a Surrogate Classification according to Tumor Grade and Immunohistochemical Biomarkers. Journal of cancer epidemiology 2014;469251.

16. Kaufman B, Wu Y, Amonkar MM, Sherrill B, Bachelot T, Salazar V, et al. Impact of lapatinib monotherapy on QOL and pain symptoms in patients with HER2+ relapsed or refractory inflammatory breast cancer. Current medical research and opinion 2010;26(5):1065–73.
17. Li N, Hao Y, Xie J, Lin PL, Koo V, Ohashi E, et al. Everolimus-Based Therapy versus Chemotherapy among Patients with HR+/HER2- Metastatic Breast Cancer: Comparative Effectiveness from a Chart Review Study. International journal of breast cancer 2015;240750.
18. Perez EA, Romond EH, Suman VJ, Jeong J, Sledge G, Geyer CE, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. Journal of clinical oncology official journal of the American Society of Clinical Oncology 2014;32(33):3744–52.

Modul 5

Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies: A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany

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REVIEW

Cost-Effectiveness of Pharmacogenomic and Pharmacogenetic Test-Guided Personalized Therapies: A Systematic Review of the Approved Active Substances for Personalized Medicine in Germany

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ABSTRACT

Background: The use of targeted therapies has recently increased. Pharmacogenetic tests are a useful tool to guide patient treatment and to test a response before administering medicines. Pharmacogenetic tests can predict potential drug resistance and may be used for determining genotype-based drug dosage. However, their cost-effectiveness as a diagnostic tool is often debatable. In Germany, 47 active ingredients are currently approved. A prior predictive test is required for 39 of these and is recommended for eight. The objective of this study was to review the cost-effectiveness (CE) of pharmacogenetic test-guided drug therapy and compare the application of drugs with and without prior genetic testing.

Methods: A systematic literature review was conducted to identify the CE and cost-utility of genetic tests. Studies from January 2000 until November 2015 were searched in 16 databases including Medline, Embase, and Cochrane. A quality assessment of the full-text publications was performed using the validated Quality of Health Economic Studies (QHES) instrument.

Results: In the majority of the included studies, the pharmacogenetic test-guided therapy represents a cost-effective/cost-saving treatment option. Only seven studies lacked a clear statement of CE or cost-savings, because of uncertainty, restriction to specific patient populations, or assumptions for comparative therapy. Moreover, the high quality of the available evidence was evaluated.

Conclusion: Pharmacogenetic testing constitutes an opportunity to improve the CE of pharmacotherapy. The CE of targeted therapies depends on various factors including costs, prevalence of biomarkers, and test sensitivity and specificity. To guarantee the CE comparability of stratified drug therapies, national and international standards for

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evaluation studies should be defined.

Keywords: Abacavir; Azathioprine; Carbamazepine; Cetuximab; Cost-effectiveness; Personalized medicine; Pharmacogenetic test; Targeted therapy

INTRODUCTION

Adverse drug reactions (ADRs) are often responsible of morbidity and mortality [1]. In the USA, it has been estimated that 106,000 deaths per year are caused by ADRs [2]. In Germany, the incidence of ADR-induced hospitalizations amounts to approximately 3.25% of overall hospitalizations, and the overall ADR treatment costs sum to €434 million per year [3]. The field of pharmacogenomics or pharmacogenetics (PG), these terms are sometimes used interchangeably [4, 5], may be a solution to reduce ADRs [6]. PG constitutes a core area of personalized medicine. The growing knowledge of genetics/genomics, and particularly the increasing understanding of the genotype–phenotype interaction, forms the basis for this personalized approach. The progress in genetic technology, characterized by faster and cheaper analytical tools, is an essential driver for personalized interventions.

Genetic analyses are the central tools in the new area of personalized medicine (often also termed stratified medicine) [7, 8]. Stratified medicine aims at classifying patients into subgroups according to genetically determined features [9]. For example, patients may be divided into groups based on the known influence of genetic parameters on drug dosage and side effects [10]. Therefore, PG uses information about a person's genetic makeup to choose the best drug as well as the medication dosage for a particular patient [11]. The concept of stratified medicine also includes screening, preventive, or therapeutic measures for a specific subgroup of a patient population [12].

Pharmacogenetic tests (PTs) can be used to characterize individual patient features at the molecular, genetic, and cellular levels [13, 14]. PT primarily focuses on identifying specific biomarkers or genetic mutations. Generally, biomarkers can provide information for diagnostic, prognostic, and predictive purposes. In a diagnostic context (especially in an oncologic setting), biomarkers are used to identify a disease or the stage of the disease [15]. The assessment of a patient's overall outcome (e.g., the probability of cancer recurrence after standard treatments) can be provided by prognostic biomarkers [16]. Furthermore, in a predictive context, biomarkers are used as an efficacy test before drug administration. This test serves the purpose of assessing the likelihood of a positive response after a potential treatment. In this context, predictive biomarkers can help to optimize drug selection, dose, and treatment duration as well as prevent ADRs [17].

The presence of genetic mutations or deletions can also be used for predictive purposes. Several studies have demonstrated that previously identified genetic mutations, such as those on the epidermal growth factor receptor (EGFR), Kirsten RAS (KRAS), and the breast cancer susceptibility gene I and II (BRCA I, BRCA II), predict resistance to treatment [18, 19]. For example, an identified EGFR gene mutation or an increased EGFR gene copy number is associated with a positive response to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) in non-small cell lung cancer (NSCLC) [20]. On the other hand, a KRAS

mutation is an important predictor for resistance to an EGFR-TKI therapy [21]. Moreover, gene mutations can also provide information for optimal drug dosage. For instance, the dosage of azathioprine (AZA) is based on the thiopurine-methyltransferase (TMPT) genotype or activity. Patients with no TMPT activity (TMPT deficient) receive no or a reduced dose of AZA, whereas the dosage of AZA administered in patients with an active TMPT differs [12, 22].

The outdated concept of "one size fits all" should be replaced by stratification and move towards a patient-oriented drug treatment [23]. However, this concept is equally connected to hopes and concerns. Potential advantages of target therapies include increasing clinical effectiveness, e.g., by improving survival [24], and improving patient safety [25]. On the other hand, there are concerns regarding the increased costs of diagnostic tests [26].

However, in recent years, an increasing number of pharmacogenomics applications have been observed [27]. Currently, 47 drugs for pharmacogenetic therapy are approved in Germany. A genetic diagnostic test prior to drug administration is required for 39 of these drugs and recommended for eight [28]. An overview of pharmacogenetic therapies is provided in supplementary file 1. The sustainability of the current trend for stratified pharmacotherapies depends on the cost-effectiveness (CE) of the treatment. The incremental cost-effectiveness ratio (ICER) is a tool to assess the CE of new interventions and is defined as the ratio of the additional costs (e.g., of a new stratified therapy vs. the standard therapy) divided by the additional benefits of the new stratified therapy vs. the standard therapy. The ICER also indicates the cost per additional benefit [e.g., life-years gained (LYG) or quality-adjusted life years gained (QALY)]. Such economic analyses are necessary for identifying therapies with the greatest health benefits at acceptable costs, as well as for the development of guidelines for an optimal and efficient treatment. The use of PTs depends on their impact on the CE of targeted therapies. As a result of the limited resources in the healthcare system and the sometimes substantial costs for active ingredients, it is important to evaluate the CEs of PT-guided targeted therapies.

For this purpose, we conducted a systematic literature review to analyze the CE of stratified pharmaceutical therapies. The review has two objectives:

1. Analyze and assess the CE of PT-guided treatments in published health-economic evaluation studies.
2. Highlight the differences and methodological characteristics of the included studies, which may influence the CE of stratified therapies.

METHODS

First, PICO elements (population–intervention–comparator–outcome) were defined in order to focus the scientific issue and facilitate the literature search (Table 1).

In November 2015, a systematic literature search was conducted using the meta-database of the German Institute for Medical Documentation and Information (DIMDI) in the following databases: ABDA, AMIS, BIOSIS Previews, Cochrane Central Register of Controlled trials, Cochrane Databases of Systematic Reviews, DAHTA-Datenbank, Database of Abstracts of Reviews of Effects, EMBASE, EMBASE Alert, ETHMED, GLOBAL Health, gms, Health Technology Assessment Database, Medline, NHS, and SciSearch. The search strategy combines economic individualized medicine-related terms with the names of active ingredients. At the time of this research, there were 42 active ingredients

Table 1 Review objective and PICO elements

Review objective	To review the economic impact of PT-guided therapies; highlight the differences and methodological characteristics of the included studies
Populations	Studies of participants who received a pharmacogenetic therapy; studies were not restricted to specific indications
Interventions/comparison	Studies that compare the application of targeted agents with prior genetic testing to those without prior genetic testing. The review is not limited to specific comparators
Outcomes	ICER (e.g., cost per QALY, cost per LYG, cost per avoided HSR/ADR)

PICO population–intervention–comparator–outcome, *QALY* quality-adjusted life year, *LYG* life-years gained, *HSR* hypersensitivity reaction, *ADR* adverse drug reaction

approved for personalized medicine in the German market [28]. The following search strategy, using combined search terms (English and German), was applied: (1) [Abacavir OR Afatinib OR Anastrozole OR Arsentrioxid OR Ataluren OR Azathioprine OR Bosutinib OR Brentuximab vedotin OR Carbamazepine OR Cetuximab OR Crizotinib OR Ceritinib OR Dabrafenib OR Dasatinib OR Eliglustat OR Erlotinib OR Everolimus OR Exemestane OR Fulvestrant OR Gefitinib OR Ibrutinib OR Imatinib OR Ivacaftor OR Lapatinib OR Letrozole OR Lomitapide OR Maraviroc OR Mercaptopurine OR Natalizumab OR Nilotinib OR Olaparib OR Oxcarbazepine OR Panitumumab OR Pertuzumab OR Ponatinib OR Tamoxifen OR Toremifene OR Trametinib OR Trastuzumab OR Trastuzumab emtansine OR Vandetanib OR Vemurafenib] **AND** (2) [Biomarker OR individuali* OR personali* OR stratif* OR Subgruppe* OR subgroup* OR pharmakogen* OR pharmacogen* OR Test* OR profiling] **AND** (3) [Nutzen OR benefit OR Nutzwert OR utility OR Effektivität OR effectiveness OR effizien* OR efficien*] **AND** (4) [Kosten* OR cost* OR technology assessment]. The operator "AND" combined the search terms while an asterisk was used as a truncation for a greater search coverage. Additionally, a search was conducted by hand. Assessment of titles and abstracts was performed independently by two researchers. Only original studies published in full text were included. Full papers were assessed by two researchers, and disagreements were resolved through discussion. Figure 1 summarizes the search process.

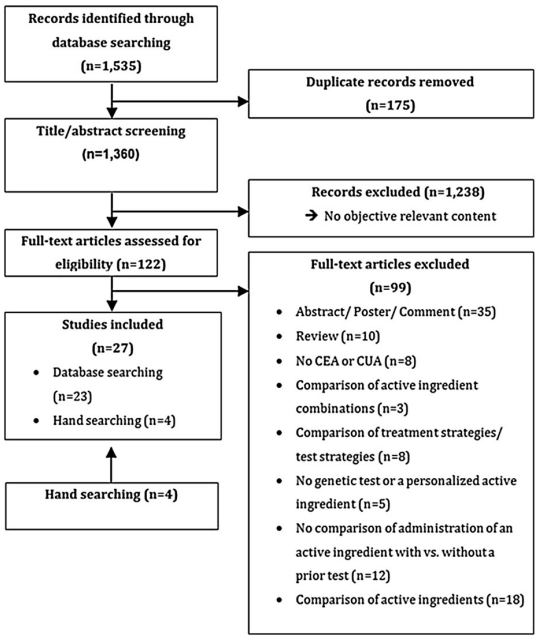

Fig. 1 Flow diagram of articles identified and evaluated on the basis of inclusion criteria

Table 2 The Quality of Health Economic Studies (QHES) instrument

Questions		Points	Yes/no
1.	Was the study objective presented in a clear, specific, and measurable manner?	7	
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	
3.	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial—best, expert opinion—worst)?	8	
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	
6.	Was incremental analysis performed between alternatives for resources and costs?	6	
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3–5%) and justification given for the discount rate?	7	
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term, and negative outcomes included?	6	
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	
15.	Were the conclusions/recommendations of the study justified and based on the study results?	8	
16.	Was there a statement disclosing the source of funding for the study?	3	
Total points			

To ensure comparability, the results were converted to US dollars at the exchange rate of the year of publication [29, 30].

The published 100-point Quality of Health Economic Studies (QHES) instrument was used to evaluate the quality of the included studies (Table 2) [31]. The QHES evaluation was also conducted by two independent researches, and the disagreements were resolved through discussion.

Table 3 Classification of study quality

Points	Study quality
0–24	Extremely poor
25–49	Poor
50–74	Fair
75–100	High

This evaluation consists of 16 items, each providing a score between one and nine. The overall evaluation, after summing the scores of each item, identified the quality of an article, which was categorized into four groups (Table 3). The evaluation of the article quality was also conducted by two independent experts.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

The database search identified 1535 records. After removing 175 duplicates, the title and abstract of the remaining 1360 records were screened. Subsequently, 1238 records were excluded as they did not cover the objective of the study. The remaining 122 records were assessed for eligibility, and inclusion criteria were fulfilled by 27 studies, which were included in the final assessment (Fig. 1).

All studies are characterized by a variety of elements, such as country, perspective, treatment line, active ingredient, treatment strategy, biomarkers, consideration of test costs, consideration of sensitivity, and specificity of the test and funding source. A detailed overview is provided in supplementary material 2.

Quality Assessment (QHES)

The results of the quality assessment using the QHES instrument are presented in Table 4. An average value of 85.81 was calculated. Three studies [46, 47, 56] were assessed to have a fair quality, while all others achieved a high quality score. The objective of all studies was represented in a clear manner (QHES item 1), but seven did not state the perspective of the study (QHES item 2) [22, 33, 37, 40, 45, 53, 56]. In three studies, data were not extracted from the best available source (QHES item 3) [32, 48, 49]. Six studies used data from a subgroup analysis (QHES item 4) [32, 36, 37, 42, 52, 53]. The majority of studies, with the exception of one, handled uncertainties properly (QHES item 5) [56]. All studies, with the exception of five, performed an incremental analysis for costs and outcomes between the alternatives (QHES item 6) [38, 39, 47, 51, 56]. Detailed information for the methodology of data extraction was not reported in four studies (QHES item 7) [37, 46, 47, 56]. The majority of studies fulfilled the criteria of QHES items 8 and 9. Only four studies did not choose the appropriate time horizon or did not discount benefits and costs beyond 1 year (QHES item 8) [43, 46, 51, 55]. Furthermore, four studies failed to measure the costs appropriately or to describe methods for estimations of quantities and unit costs clearly (QHES item 9) [41, 46, 47, 56]. All studies clearly stated the primary outcome (QHES item 10). All studies, except for three, stated valid health outcomes or gave a justification for the measurement used if other more valid and reliable measures were not available (QHES item 11) [12, 47, 48]. In most of the studies, the economic model, methods, and analyses were displayed transparently, except in four (QHES item 12) [22, 39, 46, 52]. All studies gave a justification for the choice of limitations or assumptions (QHES item 13). The authors of seven studies discussed explicitly the direction and the magnitude of the potential

Table 4 Results of the QHES assessment

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Score
van den Akker-van Marle et al. [32]	x	x	–	x	x	x	x	x	x	x	x	x	x	–	x	x	86
Behl et al. [33]	x	–	x	–	x	x	x	x	x	x	x	x	x	–	x	x	89
Blank et al. [34]	x	x	x	–	x	x	x	x	x	x	x	x	x	–	x	x	93
Blank et al. [35]	x	x	x	–	x	x	x	x	x	x	x	x	x	–	x	x	93
Carlson et al. [36]	x	x	x	x	x	x	x	x	x	x	x	x	x	–	x	x	94
Dong et al. [37]	x	–	x	x	x	x	–	x	x	x	x	x	x	–	x	x	85
Donnan et al. [38]	x	x	x	–	x	–	x	x	x	x	x	x	x	–	x	x	87
Dubinsky et al. [39]	x	x	x	–	x	–	x	x	x	x	x	–	x	x	x	–	82
Elkin et al. [40]	x	–	x	–	x	x	x	x	x	x	x	x	x	x	x	x	95
Hagaman et al. [22]	x	–	x	–	x	x	x	x	x	x	x	–	x	–	x	–	78
Hall et al. [41]	x	x	x	–	x	x	x	x	–	x	x	x	x	x	x	x	91
Hughes et al. [42]	x	x	x	x	x	x	x	x	x	x	x	x	x	–	x	–	91
Kapoor et al. [43]	x	x	x	–	x	x	x	–	x	x	x	x	x	x	x	–	89
Kauf et al. [44]	x	x	x	–	x	x	x	x	x	x	x	x	x	–	x	x	93
De Lima Lopes et al. [45]	x	–	x	–	x	x	x	x	x	x	x	x	x	x	x	x	95
Lyman et al. [46]	x	x	x	–	x	x	–	–	–	x	x	–	x	–	x	–	62
Marra et al. [47]	x	x	x	–	x	–	–	x	–	x	–	x	x	–	x	x	67
Nieves Calatrava et al. [48]	x	x	–	–	x	x	x	x	x	x	–	x	x	–	x	x	78
Oh et al. [49]	x	x	–	–	x	x	x	x	x	x	x	x	x	–	x	x	85
Plumpton et al. [50]	x	x	x	–	x	x	x	x	x	x	x	x	x	–	x	x	93
Priest et al. [51]	x	x	x	–	x	–	x	–	x	x	x	x	x	–	x	x	80
Rattanavipapong et al. [52]	x	x	x	x	x	x	x	x	x	x	x	–	x	x	x	x	92
Schackman et al. [53]	x	–	x	x	x	x	x	x	x	x	x	x	x	–	x	x	90
Shiroiwa et al. [54]	x	x	x	–	x	x	x	x	x	x	x	x	x	x	x	x	99
Thompson et al. [12]	x	x	x	–	x	x	x	x	x	x	–	x	x	–	x	x	86
Vijayaraghavan et al. [55]	x	x	x	–	x	x	x	–	x	x	x	x	x	–	x	x	86
Winter et al. [56]	x	–	x	–	–	–	–	x	–	x	x	x	x	–	x	–	58
Statement frequency	27	20	24	6	26	22	23	23	23	27	24	23	27	7	27	21	

Response to QHES assessment question: present (x) or absent (–)

bias (QHES item 14) [39–41, 43, 45, 52, 54]. All studies provided proper conclusions or recommendations based on results (QHES item 15). Finally, only six studies did not disclose the source of funding (QHES item 16) [22, 39, 42, 43, 46, 56].

Table 5 Number of studies in the main categories

Categories	Number of studies	Mean QHES score (range)
Number of included studies	27	85.81 (58–99)
Year of publication		
2002–2008	10	79.6 (58–95)
2009–2015	17	89.47 (78–99)
Therapeutic areas		
Epilepsy/neuropathic pain	3	90.00 (85–93)
HIV/AIDS	5	88.20 (78–93)
Immunology	7	76.57 (58–85)
Inflammatory bowel disease	3	73.33 (58–82)
Rheumatologic conditions (rheumatoid arthritis and systematic upus erythematosus)	2	76.00 (67–85)
IPF	1	78.00 (78)
Autoimmune disease	1	86.00 (86)
Oncology	12	89.17 (62–99)
Breast cancer (early stage)	3	82.00 (62–93)
Metastatic breast cancer	1	95.00 (95)
Metastatic colorectal cancer	4	91.75 (86–99)
Acute lymphoblastic leukemia	2	86.50 (86–87)
Advanced NSCLC	2	94.50 (94–95)
Active ingredient		
Abacavir	5	88.20 (78–91)
Azathioprine	7	76.57 (58–86)
Carbamazepine	3	90.00 (85–93)
Cetuximab	3	93.67 (89–99)
Cetuximab + panitumumab	1	86.00 (86)
Erlotinib	1	94.00 (94)
Gefitinib	1	95.00 (95)
Mercaptopurine	2	86.50 (86–87)
Tamoxifen	2	76.50 (62–91)
Trastuzumab	2	94.00 (91–95)
Biomarker		
EGFR	2	94.50 (94–95)
HER2	2	94.00 (93–95)
HLA-B*1502	2	88.50 (85–92)
HLA-B*5701	5	88.20 (78–93)
HOXB13-IL17BR	2	76.50 (62–91)
KRAS	4	91.75 (86–99)
HLA-A*31:01	1	93.00 (93)
TMPT	9	78.77 (58–87)

AIDS/HIV acquired immune deficiency syndrome/human immunodeficiency virus, *IPF* idiopathic pulmonary fibrosis, *NSCLC* non-small cell lung cancer, *EGFR* epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2, *HLA-B*1502* human leukocyte antigen B*1502, *HLA-B*5701* human leukocyte antigen B*5701, *HOXB13-IL17BR* two gene ratio, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *HLA-A*31:01* human leukocyte antigen 31:01, *TMPT* thiopurine methyltransferase

Main Characteristics of the Studies

All main characteristics of the studies are presented in Table 5. The included studies were published between 2002 and 2015. In the years 2000, 2001, and 2003 we did not find publications that satisfied the inclusion criteria. Two-thirds of the selected articles were published in the last 7 years. Furthermore, studies carried out in recent years (between 2009 and 2015) achieved a higher QHES average score than those published previously. AZA is the most frequently considered active ingredient for which PT were evaluated (seven

studies out of the 27 included here). Five of these seven evaluations were published between 2002 and 2006, and the latest article was published in 2014. TMPT, which predicts the potential effectiveness of AZA application, is the most commonly evaluated biomarker. Six of the nine studies focusing on TMPT were published between 2002 and 2006. Over two-fifth of the studies included here evaluated the CE of PT-guided therapy in oncological diseases. Table 5 shows the subdivision of the included studies according to the main categories as well as QHES average score and range in the corresponding category.

Cost-effectiveness of Pharmacogenetics Testing in Specific Therapeutic Areas

Epilepsy

The cost-effectiveness of pharmacogenetics testing in the treatment of epilepsy was evaluated in three studies. The latest study from Plumpton et al. [50] focused on the HLA*A*31:01 allele screening test. An ICER of £37,314 (US$53,674) per cutaneous avoided ADR for a prior HLA*A*31:01 allele test and carbamazepine (CBZ) administration following the test result was calculated. Studies from Dong et al. [37] and Rattanavipapong et al. [52] also examined the CE of PT prior to CBZ administration; however, these analyses aimed at identifying the presence of the HLA-B*15:02 allele. Rattanavipapong et al. [52] examined the influence of prescribing CBZ with and without prior HLA-B*15:02 allele test for epilepsy as well neuropathic pain. In the case of epilepsy, they calculated an ICER of THB 220,000 (US$7066) per QALY, while for neuropathic pain, the ICER was THB 130,000 (US$4137) per QALY, gained through PT and CBZ administration following the test results. Dong et al. [37] investigated the CE of HLA-B*15:02 allele testing prior to initiation of CBZ therapy in Singapore. In comparison with no testing and CBZ prescription to all patients, the test result-based CBZ administration achieved an ICER of US$29,750. The frequency of HLA-B*15:02 allele differs between the three major ethnical populations present in Singapore. Therefore, separate ICERs were calculated for each of these groups. The test strategy led to an ICER of US$37,030 per QALY for Singapore Chinese, an ICER of US$7930 per QALY for Singapore Malays, and an ICER of US$136,630 per QALY for Singapore Indians. Regarding the US$50,000 threshold, PT before CBZ administration is cost-effective for Singapore Malays and Singapore Chinese.

HIV/Aids

All HIV/AIDS studies included here analyzed the CE of HLA-B*57:01 allele test before abacavir (ABC) administration. Hughes et al. [42] compared the CE of HLA-B*57:01 allele test prior to ABC prescription (patients with a positive test result received an alternative treatment and patients without HLA-B*57:01 allele were treated with ABC) with that of patients treated with ABC but not tested. A dominant ICER was determined in the first group. However, the incremental CE depends on the costs of the alternative treatment: based on the costs of the highly active antiretroviral therapy (HAART) alternative, a range of dominant ICER (alternative treatment is less expensive and more effective) up to an €22,811 (US$26,714) per avoided HSR was calculated.

Schackman et al. [53] determined an ICER of US$36,700 per QALY for a previous HLA-B*57:01 allele test and a test result-based treatment in comparison with no testing.

On the other hand, Nieves Calatrava et al. [48] assessed an ICER of €630.16 (US$807) per avoided HSR, and Kauf et al. [44] calculated an

even lower ICER of only US$328 per avoided HSR for a HLA-B*57:01 allele test-based ABC treatment (as opposed to the prescription of ABC without a predictive test).

The latest published study by Kapoor et al. [43] provides a detailed analysis for HLA-B*57:01 allele testing before ABC prescription in three ethnicities. Furthermore, differential results regarding the disease stage (early and late stage) and the treatment strategy (tenofovir and ABC can be prescribed as first-line treatment while some patients were contraindicated to tenofovir) were described. For early stage treatment, where tenofovir and ABC can be prescribed as first-line, the CE for a HLA-B*57:01 allele test-based ABC treatment (in contrast to administration of ABC without testing) resulted in an ICER of US$415,845 per QALY for Han-Chinese, an ICER of US$318,029 per QALY for Southeast-Asian Malays, and ICER of US$208,231 per QALY for South-Asian Indians. For this treatment line, where both active ingredients were prescribed, a CE analysis was also performed for patients at a later stage of the disease. In the latter case, ICERs of US$926,938 per QALY for Han-Chinese, of US$624,297 per QALY for Southeast-Asian Malays, and of US$284,598 per QALY for South-Asian Indians were calculated. This study also included a CE analysis for these three patients groups contraindicated for tenofovir. For the early stage treatment group, ICERs of US$252,350 per QALY for Han-Chinese, of US$154,490 per QALY for Southeast-Asian Malays, and of US$44,649 per QALY for South-Asian Indians were analyzed. For patients at a later stage of the disease, ICERs of US$757,270 per QALY for Han-Chinese, of US$454,223 per QALY for Southeast-Asian Malays, and of US$114,068 per QALY for South-Asian Indians were found. This study indicates that a predictive test prior to ABC administration is not effective, independently of the disease stage. Exceptions are tenofovir-contraindicated early-stage patients.

Immunology

Inflammatory Bowel Diseases Winter et al. [56] conducted a CE analysis for a PT, which analyzed TMPT activity. The dosage of AZA is based on TMPT activity. Hence, a standard AZA dose without prior testing was compared to an activity-based AZA dosage administration. Costs of £487 (US$776) per LSY for a 30-year-old patient and of £951 (US$1515) for a 60-year-old patient were determined.

On the other hand, Dubinsky et al. [39] and Priest et al. [51] identified CE for a genotype test-based TMPT activity initiation of AZA, compared to administering a standard dosage of AZA without a prior predictive test. Furthermore, Priest et al. [51] compared the phenotypic and genotypic testing and showed that the phenotypic TMPT test strategy was the most cost-effective approach.

Rheumatologic Conditions (Rheumatoid Arthritis and Systematic Lupus Erythematosus) Marra et al. [47] and Oh et al. [49] evaluated the CE of PT in the therapeutic area of rheumatologic conditions. In both studies, administering a TMPT test result-based dose of AZA is more effective and less costly than administering a standard dose of AZA without prior testing.

Idiopathic Pulmonary Fibrosis Hagaman et al. [22] evaluated the CE of TMPT testing in idiopathic pulmonary fibrosis. The performance of a TMPT test and the test result-based AZA dosage (in contrast to the administration of a standard dose AZA without prior TMPT test) resulted in an ICER of US$29,663 per QALY.

Autoimmune Disease Thompson et al. [12] investigated the CE of TMPT testing prior to AZA administration in autoimmune diseases. An incremental cost of £421.06 (US$625) and an incremental net benefit of £256.89 (US$381) for TMPT activity test prior to AZA administration (in contrast to the administration of a standard dose of AZA without TMPT test) were determined.

Oncology

Breast Cancer (Early Stage) Lyman et al. [46] investigated the CE of PT in early stage breast cancer relative to the recurrence of the disease. A comparison between testing the risk of relapse and administration of the standard therapy, consisting of tamoxifen and chemotherapy, was conducted. Patients at low risk of relapse only received tamoxifen, the others tamoxifen and chemotherapy. Lyman et al. [46] determined an ICER of US$3385 per LYS (no indication of age), whereas Hall et al. [41] indicate an ICER of US$8852 per QALY (patients above 60 years of age). In this study, Hall et al. [41] concluded that a general statement on the cost-effectiveness could not be made because of substantial uncertainties.

Blank et al. [34] investigated the CE of PT in early stage breast cancer prior to administration of trastuzumab. In this study a comparison of a test result-based administration of trastuzumab and the administration of the drug without a prior test was conducted. In the test strategy, patients with proven HER2 overexpression received trastuzumab, whereas patients without HER2 overexpression received an alternative therapy. Two testing procedures were considered: immunohistochemistry (IHC test) and fluorescence in situ hybridization (FISH test). The therapy with both tests alone or in combination (compared with no previous test) had significantly lower costs, but the FISH test alone was considered the most cost-effective approach. However, administering trastuzumab with no previous test achieved a higher benefit, as a result of the imperfect sensitivity and specificity of the tests. A CE ratio was not calculated.

Metastatic Breast Cancer Elkin et al. [40] evaluated the CE of PT prior to trastuzumab administration in metastatic breast cancer. HER2 overexpression test prior to trastuzumab prescription was compared with the prescription of trastuzumab and chemotherapy without a predictive test. Patients with HER2 overexpression received a combination treatment, consisting of trastuzumab and chemotherapy. Patients without HER2 overexpression only received chemotherapy. In this study, IHC and FISH tests were used to determine HER2 overexpression. The use of a FISH test resulted in a dominant ICER. Furthermore, performing the IHC test before the FISH test was the most cost-effective approach. However, the benefit provided by this strategy compared to trastuzumab administration without prior test was less.

Metastatic Colorectal Cancer Shiroiwa et al. [54] analyzed the CE of a PT prior administration of cetuximab in metastatic colorectal cancer. A comparison of KRAS mutation test and a result-based administration of cetuximab (patients with wild-type KRAS received cetuximab and patients with KRAS mutations received best supportive care, BSC) and cetuximab treatment without a predictive test were conducted. A dominant ICER for the testing strategy was determined.

Vijayaraghavan et al. [55] determined the cost-effectiveness of a KRAS mutation test prior to administration of cetuximab monotherapy,

treatment with cetuximab in combination with chemotherapeutics, and panitumumab monotherapy. Patients with a KRAS mutation received exclusively chemotherapeutics in combination therapy and BSC for monotherapy. The use of a KRAS mutation test before prescription of cetuximab monotherapy, panitumumab monotherapy, and cetuximab combination therapy achieved a dominant ICER compared to the treatment without the predictive test.

Blank et al. [35] evaluated the CE for a KRAS mutation test and a subsequent BRAF gene test before administration of cetuximab in combination with BSC for metastatic colorectal cancer. Patients with a KRAS or BRAF mutation received exclusively BSC. The subsequent verification of BRAF status after KRAS test was the most cost-effective approach compared to treating all patients without testing or solely after the KRAS test. However, perhaps as a result of the imperfect sensitivity and specificity, there was a higher benefit in prescribing cetuximab without a prior test compared with the test strategies. An ICER for a predictive test prior cetuximab administration as compared to without prior testing and treating all patients with cetuximab was not reported.

Behl et al. [33] also evaluated the CE of a subsequent BRAF gene test in addition to a KRAS mutation analysis prior to cetuximab administration in combination with BSC. The subsequent verification of BRAS status after the KRAS test was also the most cost-effective approach. However, even in this case, perhaps as a result of the imperfect sensitivity and specificity of the testing procedures, cetuximab without a prior test led to a higher benefit. An ICER was not stated.

Acute Lymphoblastic Leukemia Van den Akker-van Marle et al. [32] conducted a CE study for a PT prior to mercaptopurine administration in acute lymphoblastic leukemia in children. There, an ICER of €4800 (US$5702) per LYG for a genotypic TMPT activity test and TMPT activity-based mercaptopurine dosage, compared to no testing and administration of a standard initial dose of mercaptopurine, was determined.

On the other hand, in the study by Donnan et al. [38] neither a phenotypic nor a genotypic test for determining TMPT activity prior to mercaptopurine administration proved to be cost-effective (higher costs for the same benefit).

Advanced Non-Small Cell Lung Cancer Carlson et al. [36] conducted a CE study for a PT prior to erlotinib administration in advanced non-small cell lung cancer patients. A comparison was made between the use of an EGFR test and the result-based erlotinib administration in patients with EGFR mutations or an alternative therapy for patients without EGFR mutation, and the treatment of all patients with erlotinib without a prior test. An ICER of US$162,018 per QALY for the use of a gene copy number test was determined. The ICER clearly surpassed that of the study set threshold of US$100,000 to US$150,000 per QALY.

De Lima Lopes et al. [45] evaluated the cost-effectiveness of the EGFR test prior to gefitinib prescription. A dominant ICER for the comparison of the use of an EGFR test prior to gefitinib administration and no testing while prescribing chemotherapy with subsequent gefitinib administration was determined. In the test strategy, patients with an EGFR mutation received gefitinib followed by chemotherapy as second-line therapy. Patients without EGFR mutation received chemotherapy with subsequent BSC.

Main Results of This Systematic Review

In this systematic review, six main results were obtained:

1. In the majority of studies, a PT-guided administration of an active ingredient was found to be cost-effective or leads to cost savings.
2. A general statement on CE for a test-guided application of an active ingredient (independently of the indication for which it has been prescribed) was not observed.
3. The majority of studies analyzed the CE of targeted therapies in oncological diseases.
4. The CE depends on various factors (e.g., prevalence of biomarkers, test costs, threshold value, prevalence of ADRs, response rate of therapy).
5. The CE of a PT-guided therapy can differ between indications as well as within the same indication.
6. The results depend on the perspective of the study (society, healthcare system, and payer).

DISCUSSION

This comprehensive review analyzed the CE of PT-guided therapies. For this propose we included only studies that compared the CE of the administration of an active ingredient with or without a prior predictive test. PTs serve to determine the effectiveness of active ingredients, to take a therapeutic decision, and ultimately to optimize patient benefit by avoiding ADRs. Preventing ADRs leads to an increase in drug safety and is therefore the central argument for the application of PTs [57, 58]. However, the usefulness of such pharmacogenetic tools depends on their CE. CE analyses are essential for reimbursement decisions of new technologies as well as pricing by decision-makers. This review investigated whether PTs contribute to an efficient therapy management.

An average value of 85.81 for all 27 assessed studies was calculated. The evaluation through the QHES instrument is a quality assessment regarding the methodology of the studies. This evaluation considered the specific stratified medicine inadequate. Important criteria in the assessment of PTs are the prevalence of biomarkers, sensitivity, and specificity of the test, as well testing costs.

Generally, innovations are used if they have a significant influence on the outcomes (e.g., on the survival or on the improvement in the quality of life). As a result of the limited healthcare budget, it is essential to assess the additional benefits of the innovation in comparison with previous standards. Therefore, CE analyses are necessary and were used for reimbursement decisions. The CE of a medical intervention depends on whether it will be able to provide benefits at a reasonable cost. CE analyses estimate the ICER of interventions. ICER is an analytical tool of the CE analysis (CEA), which compares the differences in cost of two treatments based on their different outcomes (e.g., new treatment vs. previous treatment). Threshold values vary from country to country. For example, a threshold of US$50,000 is stated as cost-effective in the USA [59]. An intervention with an ICER of less than US$50,000 per additional QALY is classified as cost-effective. The CE depends on several factors. In this comprehensive review some divergent features in the study design, which influenced the CE, were identified.

Perspective of the study The CE of a study depends, among other things, on the chosen

perspective (e.g., healthcare system, society) [60]. The missing consideration of indirect cost allows no final assessment and comprehensive interpretation. Ideally, the cost should be collected from a societal perspective. However, for this purpose, the required costs are difficult to quantify (e.g., loss of wages) [61].

Time horizon/discounting Different CE values arise because of the various time horizons. For the consideration of ADRs, a time horizon of 1 year would be sufficient. This is because ADRs caused by pharmacogenetic applications immediately appear after the active ingredient has been administered [62]. A defined time horizon would lead to an improved comparability. In contrast, for the consideration of pharmacodynamic effects, a life-long time horizon should be considered, since the costs for long-term consequences or the avoidance of them have a considerable importance.

Impact of sensitivity and specificity of the test procedures Weaknesses in the sensitivity and specificity of the predictive tests may influence the CE of a strategy. Sensitivity and specificity are characterized by a great heterogeneity. This could lead to an incorrect classification as responder or non-responder. Thus, it may result in the administration of ineffective drugs, undesirable effects, or the exclusion of an effective therapy. Generally, this implies losses of effectiveness for the relevant therapy.

Prevalence of biomarkers Biomarker prevalence in the specific study populations is based on different assumptions. Dong et al. [37] differentiated the study population according to allele frequencies. The HLA-B*1502 allele frequencies differ between various ethnic groups. The corresponding classification leads to an increased degree of stratification. Fundamentally, a lower biomarker prevalence leads to a lower CE of the PT [63]. According to the lower likelihood to identify a responder, the overall benefit is low. Homogenous groups enable an increase in test validity or the likelihood to identify a responder, as well as the examination of biomarker prevalence values by sensitivity analysis.

Costs of testing procedures Various yearly prices, countries, test characteristics, lack of transparency on test prices, as well as often used estimates, reduce the possibility of comparing the costs of testing procedures. Sensitivity analyses of the price may reduce the incomparableness. Possible future cost reductions of PTs will have a positive impact on the CE.

Lack of evidence-based data The data used for CE evaluations are partially of insufficient quality and quantity. The evaluations often derived from retrospective studies. Randomized controlled trials (RCT) enable the generation of evidence-based data and provide a valid basis for CEA. RCTs are regarded as the gold standard of data collection [64, 65]. The main problems in this context are low funding, low interest in clinical trials (except studies for approved medications), small patient populations, as well as lack of valid discoveries [66]. It is difficult to conduct an RCT for pharmacogenetic applications. The anticipated differences in treatment effectiveness accompanying the test strategies and the need to generate significant outcomes in patients with a similar genotype require large group sizes [67].

Oncology is the most frequently discussed disease area for CEA. This indication area is characterized by the high toxicity of chemotherapeutic agents as well as poor clinical outcomes [68, 69]. This raises the potential to be one of the largest and most attractive fields for pharmacogenomics application. Oncology is particular well suited to show CE, because it is an area with a large

number of affected patients and with expensive cancer-associated outcomes (chronic pain, ADRs, death). Minor improvements of outcomes affect the CE, because expensive outcomes such as long hospital stays can be prevented.

There are some economic, clinical, and practical challenges in connection with the development and the application of PTs. Research and development of pharmacogenetic applications is characterized by some regulatory challenges [70, 71] and high costs to prove clinical benefits [72]. There is a disincentive for pharmaceutical companies to invest in companion diagnostics [73, 74]: an investment into a market without free pricing is a risk for pharmaceutical companies. Genetic analyses (subgroup analysis) divide the market and reduce the total turnover. In countries without the possibility of dynamic pricing or changes in price according to subgroups or indications, the different value of PTs for the specific subgroups is appropriate. A general problem of personalized medicine is the development of drugs for small patient groups but with the same costs of the research and development needed for the development of drugs for larger groups [75]. The danger of low total turnover by small user groups hinders further research and development in the field of targeted therapies. Therefore, in areas with larger market segmentations, pharmacogenetic research should be financed by public resources [76]. Moreover, payers link pharmacogenetic applications with concerns. PTs as well as proteomic tests seem to be more expensive than conventional diagnostic and prognostic tools [77]. Actually, only a few pharmacogenetic examinations were financed within the uniform value scale, on the basis of pricing of ambulant services (EBM). Performing a PT for eight of 47 active ingredients is not compulsory. For 10 of these 47 active ingredients CEA were conducted. The insufficient basis for a conclusion can be used as a reason for the restrained reimbursement for PTs.

Furthermore, the clinical benefit of an intervention (e.g., CE, net benefit) is an essential prerequisite for PT application. However, because of the lack of evidence for the correlation between the influence of a PT on the clinical outcome [78], it is difficult to prove the benefit. No test can perfectly predict whether a patient will respond positively to a particular treatment. Various factors influence the therapeutic outcome. Generally, ADRs often occur immediately after treatment [79]. Thus, the outcomes (e.g., cost per avoided ADR) can be quickly and easily observed [61], especially in oncological studies. Moreover, the effects also depend on monitoring ADR quality.

Some practical challenges are connected with the routine use of PT. The partly missing reimbursement [27, 80], the lack of clinical guidelines [81], and the processing time associated with treatment delays [82] preclude their widespread application. Furthermore, the use of PT essentially depends on its acceptance by physicians [83]. The restrained use of PT is the result of the missing clinical validation for the clinical application as well of the missing practical and standardized guidelines [84]. There are also ethical concerns regarding the use of PT. Patients were excluded from target therapies as a result of the test results. The insufficient sensitivity and specificity of PTs may lead to a wrong stratification and therefore to the lack of an effective treatment.

The costs of the tests and which savings could be achieved through the use of predictive tests must be known. If there are higher savings, it is economically sensible to conduct a PT. In modelling the CE of PT, important factors such as the sensitivity and specificity of these tests,

degree of gene penetrance, association between genotype and clinical outcome, genotype prevalence in the population, likelihood for ADR, and survival according to the genotype and the treatment strategy should be considered.

The quality assessment through the QHES may be subjective and may represent a major limitation of this study. The assessment of study aspects is easy to determine. In contrast, aspects which aim to evaluate the adequacy are characterized by variances. Therefore, two researchers performed the assessment independently to minimize this subjectivity of the QHES instrument.

National and international standards for the assessment of PT should be defined and implemented to improve the quality of the study. Uncertainties may be decreased by more accurate estimations of effectiveness and costs [85]. Furthermore, an independent financing system (e.g., public financing) could enhance the credibility of the results. Such studies are focusing not solely on effectiveness but also on efficiency.

CONCLUSION

The application of personalized therapies is partly associated with high economic costs. This review has demonstrated that, in the majority of the studies included here, test-guided personalized therapies are more cost-effective than non-test-guided personalized therapies. Hence, a prior test before drug administration seems to be useful for therapeutic decisions, dosing according to the different genotypes or gene activity, and/or reducing adverse drug reactions. However, the results of the studies are mainly influenced, e.g., by sensitivity and specificity of the test procedures, prevalence of biomarkers, and the perspective of the study. Generally, analyses of the CE are an essential part of the reimbursement recommendations. However, to guarantee a comparability of CE of stratified drug therapies, national and international standards for evaluations studies should be defined.

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REFERENCES

1. Alomar MJ. Factors affecting the development of adverse drug reactions (review article). Saudi Pharm J. 2014;22:83–94.
2. US Food and Drug Administration (FDA). Preventable adverse drug reactions: a focus on drug interactions. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm. Accessed 28 Apr 2016.
3. Rottenkolber D, Schmiedl S, Rottenkolber M, et al. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. Pharmacoepidemiol Drug Saf. 2011;20:626–34.
4. Rodríguez-Vicente AE, Lumbreras E, Hernández JM, et al. Pharmacogenetics and pharmacogenomics as tools in cancer therapy. Drug Metabol Personal Ther. 2016;31:25–34.
5. Weng L, Zhang L, Peng Y, Huang RS. Pharmacogenetics and pharmacogenomics: a bridge to individualized cancer therapy. Pharmacogenomics. 2013;14:315–24.
6. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. JAMA. 2001;286:2270–9.
7. Schleidgen S, Klingler C, Bertram T, Rogowski WH, Marckmann G. What is personalized medicine: sharpening a vague term based on a systematic literature review. BMC Med Ethics. 2013;14:55.
8. FDA. Paving the way for personalized medicine: FDA's role on a new era of medical product development. 2013. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf. Accessed 04 Apr 2016.
9. Ondra T, Dmitrienko A, Friede T, et al. Methods for identification and confirmation of targeted subgroups in clinical trials: a systematic review. J Biopharm Stat. 2016;26:99–119.
10. Ma Q, Lu AYH. Pharmacogenetics, pharmacogenomics, and individualized medicine. Pharmacol Rev. 2011;63:437–59.
11. National Human Genome Research Institute. Frequently asked questions about pharmacogenomics. 2014. http://www.genome.gov/27530645. Accessed 2 May 2016.
12. Thompson AJ, Newman WG, Elliott RA, Roberts SA, Tricker K, Payne K. The cost-effectiveness of a pharmacogenetic test: a trial-based evaluation of TPMT genotyping for azathioprine. Value Health. 2014;17:22–33.
13. Scott SA. Personalizing medicine with clinical pharmacogenetics. Genet Med. 2011;13:987–95.
14. Mini E, Nobili S. Pharmacogenetics: implementing personalized medicine. Clin Cases Miner Bone Metab. 2009;6(1):17–24.
15. National Cancer Institute. Tumor markers. 2015. http://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet. Accessed 31 Mar 2016.
16. Mehta S, Shelling A, Muthukaruppan A, et al. Predictive and prognostic molecular markers for cancer medicine. Ther Adv Med Oncol. 2010;2:125–48.
17. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. N Engl J Med. 2011;364:1144–53.
18. Stewart EL, Tan SZ, Liu G, Tsao M. Known and putative mechanisms of resistance to EGFR targeted therapies in NSCLC patients with EGFR mutations-a review. Transl Lung Cancer Res. 2015;4:67–81.
19. Norquist B, Wurz KA, Pennil CC, et al. Secondary somatic mutations restoring BRCA1/2 predict chemotherapy resistance in hereditary ovarian carcinomas. J Clin Oncol. 2011;29:3008–15.
20. Takano T, Ohe Y, Sakamoto H, et al. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. J Clin Oncol. 2005;23:6829–37.
21. Massarelli E, Varella-Garcia M, Tang X, et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. Clin Cancer Res. 2007;13:2890–6.
22. Hagaman JT, Kinder BW, Eckman MH. Thiopurine S-methyltransferase [corrected] testing in idiopathic pulmonary fibrosis: a pharmacogenetic cost-effectiveness analysis. Lung. 2010;188:125–32.
23. Vogenberg FR, Barash CI, Pursel M. Personalized medicine: part 1: evolution and development into theranostics. Pharm Ther. 2010;35(10):560–76.

24. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372:30–9.

25. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov. 2007;6:287–93.

26. AJMC. Balancing innovation with cost in diagnostic testing. 2015;21(12):SP425. http://www.ajmc.com/journals/evidence-based-oncology/2015/august-2015/balancing-innovation-with-cost-in-diagnostic-testing. Accessed 31 Mar 2016.

27. Johnson JA. Pharmacogenetics in clinical practice: how far have we come and where are we going? Pharmacogenomics. 2013;14:835–43.

28. The German Assoziation of Research-based Pharmaceutical Companies (VFA). Pharmakogenetik 24. February 2016 Approved drugs for personalized medicine in Germany. http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/individualisierte-medizin.html. Accessed 1 Apr 2016.

29. Organisation for Economic Co-Operation and Development (OECD). StratExtracts: PPPs and exchange rates. https://stats.oecd.org/Index.aspx?DataSetCode=SNA_TABLE4#. Accessed 1 Apr 2016.

30. Currency Exchange. Exchange rate US dollar (USD) to Thailand baht (THB). http://usd.de.fx-exchange.com/thb/. Accessed 1 Apr 2016.

31. Chiou C-F, Hay JW, Wallace JF. Development and validation of grading system for quality of cost-effectiveness studies. Med Care. 2003;41(1):32–44.

32. van den Akker-van Marle M, Elske Gurwitz D, Detmar SB, et al. Cost-effectiveness of pharmacogenomics in clinical practice: a case study of thiopurine methyltransferase genotyping in acute lymphoblastic leukemia in Europe. Pharmacogenomics. 2006;7:783–92.

33. Behl AS, Goddard Katrina A B, Flottemesch TJ, et al. Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer. J Natl Cancer Inst. 2012;104:1785–95.

34. Blank PR, Schwenkglenks M, Moch H, Szucs TD. Human epidermal growth factor receptor 2 expression in early breast cancer patients: a Swiss cost-effectiveness analysis of different predictive assay strategies. Breast Cancer Res Treat. 2010;124:497–507.

35. Blank PR, Moch H, Szucs TD, Schwenkglenks M. KRAS and BRAF mutation analysis in metastatic colorectal cancer: a cost-effectiveness analysis from a Swiss perspective. Clin Cancer Res. 2011;17:6338–46.

36. Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer. Value Health. 2009;12:20–7.

37. Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology. 2012;79:1259–67.

38. Donnan JR, Ungar WJ, Mathews M, Hancock-Howard RL, Rahman P. A cost effectiveness analysis of thiopurine methyltransferase testing for guiding 6-mercaptopurine dosing in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2011;57:231–9.

39. Dubinsky MC, Reyes E, Ofman J, Chiou C, Wade S, Sandborn WJ. A cost-effectiveness analysis of alternative disease management strategies in patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. Am J Gastroenterol. 2005;100:2239–47.

40. Elkin EB, Weinstein MC, Winer EP, Kuntz KM, Schnitt SJ, Weeks JC. HER-2 testing and trastuzumab therapy for metastatic breast cancer: a cost-effectiveness analysis. J Clin Oncol. 2004;22:854–63.

41. Hall PS, McCabe C, Stein RC, Cameron D. Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer. J Natl Cancer Inst. 2012;104:56–66.

42. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. Pharmacogenetics. 2004;14:335–42.

43. Kapoor R, Martinez-Vega R, Dong Di, et al. Reducing hypersensitivity reactions with HLA-B*5701 genotyping before abacavir prescription: clinically useful but is it cost-effective in Singapore? Pharmacogenet Genomics. 2015;25:60–72.

44. Kauf TL, Farkouh RA, Earnshaw SR, Watson ME, Maroudas P, Chambers MG. Economic efficiency of genetic screening to inform the use of abacavir sulfate in the treatment of HIV. Pharmacoeconomics. 2010;28:1025–39.

45. de Lima Lopes G, Segel JE, Tan DSW, Do YK, Mok T, Finkelstein EA. Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung. Cancer. 2012;118:1032–9.

46. Lyman GH, Cosler LE, Kuderer NM, Hornberger J. Impact of a 21-gene RT-PCR assay on treatment decisions in early-stage breast cancer: an economic analysis based on prognostic and predictive validation studies. Cancer. 2007;109:1011–8.

47. Marra CA, Esdaile JM, Anis AH. Practical pharmacogenetics: the cost effectiveness of screening for thiopurine s-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. J Rheumatol. 2002;29:2507–12.

48. Nieves Calatrava D, de la Calle-Martín O, Iribarren-Loyarte JA, et al. Cost-effectiveness analysis of HLA-B*5701 typing in the prevention of hypersensitivity to abacavir in HIV+ patients in Spain. Enferm Infecc Microbiol Clin. 2010;28:590–5.

49. Oh K, Anis AH, Bae S. Pharmacoeconomic analysis of thiopurine methyltransferase polymorphism screening by polymerase chain reaction for treatment with azathioprine in Korea. Rheumatology (Oxford). 2004;43:156–63.

50. Plumpton CO, Yip VLM, Alfirevic A, Marson AG, Pirmohamed M, Hughes DA. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia. 2015;56:556–63.

51. Priest VL, Begg EJ, Gardiner SJ, et al. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. Pharmacoeconomics. 2006;24:767–81.

52. Rattanavipapong W, Koopitakkajorn T, Praditsitthikorn N, Mahasirimongkol S, Teerawattananon Y. Economic evaluation of HLA-B*15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand. Epilepsia. 2013;54:1628–38.

53. Schackman BR, Scott CA, Walensky RP, Losina E, Freedberg KA, Sax PE. The cost-effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. AIDS. 2008;22:2025–33.

54. Shiroiwa T, Motoo Y, Tsutani K. Cost-effectiveness analysis of KRAS testing and cetuximab as last-line therapy for colorectal cancer. Mol Diagn Ther. 2010;14:375–84.

55. Vijayaraghavan A, Efrusy MB, Göke B, Kirchner T, Santas CC, Goldberg RM. Cost-effectiveness of KRAS testing in metastatic colorectal cancer patients in the United States and Germany. Int J Cancer. 2012;131:438–45.

56. Winter J, Walker A, Shapiro D, Gaffney D, Spooner RJ, Mills PR. Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2004;20:593–9.

57. Alagoz O, Durham D, Kasirajan K. Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions. Pharmacogenomics J. 2016;16:129–36.

58. Wei C, Lee MM, Chen Y. Pharmacogenomics of adverse drug reactions: implementing personalized medicine. Hum Mol Genet. 2012;21:R58–65.

59. Eichler H, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health. 2004;7:518–28.

60. Owens DK. Interpretation of cost-effectiveness analyses. J Gen Intern Med. 1998;13:716–7.

61. Flowers CR, Veenstra D. The role of cost-effectiveness analysis in the era of pharmacogenomics. Pharmacoeconomics. 2004;22:481–93.

62. Atkinson AJ. Principles of clinical pharmacology. San Diego: Academic; 2012.

63. Atherly AJ, Camidge DR. The cost-effectiveness of screening lung cancer patients for targeted drug sensitivity markers. Br J Cancer. 2012;106:1100–6.

64. Akobeng AK. Understanding randomised controlled trials. Arch Dis Child. 2005;90:840–4.

65. Sullivan GM. Getting off the "gold standard": randomized controlled trials and education research. J Grad Med Educ. 2011;3:285–9.

66. Moaddeb J, Haga SB. Pharmacogenetic testing: current evidence of clinical utility. Ther Adv Drug Saf. 2013;4:155–69.

67. Ross S, Anand SS, Joseph P, Paré G. Promises and challenges of pharmacogenetics: an overview of study design, methodological and statistical issues. JRSM Cardiovasc Dis. 2012;1(1):2.

68. Bovelli D, Plataniotis G, Roila F. Cardiotoxicity of chemotherapeutic agents and radiotherapy-related

heart disease: ESMO clinical practice guidelines. Ann Oncol. 2010;21(Suppl 5):v277–82.

69. Osumi H, et al. All RAS mutation predict for poor clinical outcomes after metastasectomy in patients with metastatic colorectal cancer. 2015. http://oncologypro.esmo.org/Meeting-Resources/World-GI-2015/All-RAS-mutation-predict-for-poor-clinical-outcomes-after-metastasectomy-in-patients-with-metastatic-colorectal-cancer. Accessed 1 Apr 2016.

70. March R, Cheeseman K, Doherty M. Pharmacogenetics-legal, ethical and regulatory considerations. Pharmacogenomics. 2001;2:317–27.

71. McKinnon RA, Ward MB, Sorich MJ. A critical analysis of barriers to the clinical implementation of pharmacogenomics. Ther Clin Risk Manag. 2007;3:751–9.

72. Surendiran A, Pradhan SC, Adithan C. Role of pharmacogenomics in drug discovery and development. Indian J Pharmacol. 2008;40:137–43.

73. Academy of Medical Sciences. Optimizing stratified medicines R & D: addressing scientific and economic issues. London: Academy of Medical Sciences; 2007.

74. Padmanabhan S. Pharmacogenomics and stratified medicine. In: Handbook of pharmacogenomics and stratified medicine: London: Elsevier; 2014. p. 3–25.

75. Nuffield Council on Bioethics. Pharmacogenetics: ethical issues. London: Nuffield Council on Bioethics; 2003.

76. Deverka PA. Pharmacogenomics, evidence, and the role of payers. Public Health Genomics. 2009;12:149–57.

77. Dasgupta A. Resolving erroneous reports in toxicology and therapeutic drug monitoring: a comprehensive guide. Hoboken: Wiley; 2012.

78. Kitzmiller JP, Groen DK, Phelps MA, Sadee W. Pharmacogenomic testing: relevance in medical practice: why drugs work in some patients but not in others. Cleve Clin J Med. 2011;78:243–57.

79. Frew A. General principles of investigating and managing drug allergy. Br J Clin Pharmacol. 2011;71:642–6.

80. Huang RS, Ratain MJ. Pharmacogenetics and pharmacogenomics of anticancer agents. CA Cancer J Clin. 2009;59:42–55.

81. Mrazek DA, Lerman C. Facilitating clinical implementation of pharmacogenomics. JAMA. 2011;306:304–5.

82. Haga SB, Tindall G, O'Daniel JM. Professional perspectives about pharmacogenetic testing and managing ancillary findings. Genet Test Mol Biomark. 2012;16:21–4.

83. Rogausch A, Prause D, Schallenberg A, Brockmöller J, Himmel W. Patients' and physicians' perspectives on pharmacogenetic testing. Pharmacogenomics. 2006;7:49–59.

84. Lee S, McLeod HL. Pharmacogenetic tests in cancer chemotherapy: what physicians should know for clinical application. J Pathol. 2011;223:15–27.

85. Cooper NJ, Sutton AJ, Ades AE, Paisley S, Jones DR. Use of evidence in economic decision models: practical issues and methodological challenges. Health Econ. 2007;16:1277–86.

Supplementary Material 1: Approved personalized drugs

active ingredient	therapeutic area	testing of	test description	recommended or obligate test
Abacavir	HIV	Adverse effects	HLA-B*5701	Compulsory test since 02/2008
Afatinib	Lung cancer	Effectiveness	EGFR	Compulsory test since 09/2013
Anastrozole	Breast cancer	Effectiveness	Hormone receptor positive breast cancer cells	Compulsory test since 06/1996
Arsenic trioxide	Acute promyelocytic leukaemia	Effectiveness	Promyelocytic leukaemia-/Retinoic acid receptor alpha (PML/RAR-alpha) gene	Compulsory test since 03/2002
Ataluren	Duchenne muscular dystrophy	Effectiveness	Nonsense-Mutation of the dystrophy -gene	Compulsory test since 07/2014
Azathioprine	Immunosuppressant	Adverse effects	TMPT	Recommended
Blinatumomab	Acute lymphatic leukaemia	Effectiveness	Philadelphia-Chromosome	Compulsory test since 11/2015
Bosutinib	Chronic myelogenous leukaemia	Effectiveness	Philadelphia-Chromosome	Compulsory test since 03/2013
Brentuximab vedotin	Hodgkin Lymphomas and anaplastic large cell lymphoma	Effectiveness	Test of CD30 overexpression	Compulsory test since 10/2012
Carbamazepine	Epilepsy	Adverse effects	HLA-B*1502-allele	Recommended
Ceritinib	Lung cancer	Effectiveness	Anaplastic lymphoma kinase (ALK)	Compulsory test since 05/2015
Cetuximab	Colorectal cancer	Effectiveness	Non-mutated (wild-type) RAS-gene	Compulsory test since 07/2008
Cobimetinib	Melanoma	Effectiveness	BRAF V600 mutation	Compulsory test since 11/2015
Crizotinib	Lung cancer	Effectiveness	EML4-ALK	Compulsory test since 10/2012
Dabrafenib	Melanoma	Effectiveness	BRAF V600 mutation	Compulsory test since 08/2013
Dasatinib	Acute lymphatic leukaemia	Effectiveness	Philadelphia-Chromosome	Compulsory test since 11/2006
Eliglustat	Gaucher Disease	Effectiveness	Cytochrome-P450 Type 2D6 (CYP2D6)	Compulsory test since 01/2015
Erlotinib	Lung cancer	Effectiveness	EGFR	Compulsory test since 08/2011
Everolimus	Breast cancer	Effectiveness	HER2/neu-expression	Compulsory test since 07/2012
Exemestane	Breast cancer	Effectiveness	Estrogen receptor positive breast cancer cells	Compulsory test since 12/1999
Fulvestrant	Breast cancer	Effectiveness	Hormone receptor positive breast cancer cells	Compulsory test since 03/2004
Gefitinib	Lung cancer	Effectiveness	EGFR	Compulsory test since 07/2009
Ibrutinib	Chronic lymphatic leukaemia	Effectiveness	Deletion or TP53-mutation	Compulsory test since 10/2014
Imatinib	Acute lymphatic and chronic myelogenous leukaemia	Effectiveness	Philadelphia-Chromosome	Compulsory test since 11/2001
Ivacaftor	Mucoviscidosis with specific mutations	Effectiveness	Specific mutation of the CFTR-gene	Compulsory test since 07/2012
Lapatinibe	Breast cancer	Effectiveness	HER2–overexpression	Compulsory test since 06/2008
Letrozol	Breast cancer	Effectiveness	Hormone receptor positive breast cancer cells	Compulsory test since 01/1997
Lomitapide	Increased cholesterol- or blood lipid level	Effectiveness	Genetic evidence of homozygous familial hypercholesterolemia	Recommended test since 07/2013
Lumacaftor/Ivacaftor	Mucoviscidosis	Effectiveness	Homozygous F508del-mutation in the CFTR-gene	Compulsory test since 11/2015
Maraviroc	HIV	Effectiveness	CCR5-tropic HI-viruses	Compulsory test since 09/2007
Mercaptopurine	Acute lymphatic leukaemia	Adverse effects	TMPT	Recommended
Natalizumab	Multiple sclerosis	Adverse effects	Anti-JCV-antibody	Recommended test since 06/2011
Necitumumab	Non-small cell lung cancer	Effectiveness	EGFR	Compulsory test since 02/2016
Nilotinib	Chronic myelogenous leukaemia	Effectiveness	Philadelphia-Chromosome	Compulsory test since 11/2007
Olaparib	Ovarian cancer	Effectiveness	BRCA	Compulsory test since 12/2014
Osimertinib	Non-small cell lung cancer	Effectiveness	EGFR	Compulsory test since 02/2016
Oxcarbazepine	Epilepsy	Adverse effects	HLA-B*1502-Allele	Recommended test since 07/2012
Panitumumab	Colorectal cancer	Effectiveness	Non-mutated (wild-type) RAS-gene	Compulsory test since 12/2007
Pertuzumab	Breast cancer	Effectiveness	HER2 –overexpression	Compulsory test since 03/2013
Ponatinib	Acute lymphatic leukaemia	Effectiveness	Philadelphia-Chromosome	Compulsory test since 07/2013
Tamoxifen	Breast cancer	Effectiveness	Hormone receptor positive breast cancer cells	Recommended
Toremifen	Breast cancer	Effectiveness	Hormone receptor positive breast cancer cells	Compulsory test since 02/1996
Trametinib	Melanoma	Effectiveness	BRAF V600-mutation	Compulsory test since 06/2014
Trastuzumab	Breast cancer und gastric cancer	Effectiveness	HER2 –overexpression, HER2, gene copy number	Compulsory test since 08/2000
Trastuzumab emtansin	Breast cancer	Effectiveness	HER2 –overexpression	Compulsory test since 11/2013
Vandetanib	Medullary carcinoma of the thyroid	Effectiveness	RET-mutation	Recommended test since 02/2012
Vemurafenib	Melanoma	Effectiveness	BRAF-V600 mutation	Compulsory test since 02/2012

Supplementary Material 2: Summary of the included publications

Author (publication year)	Country/ perspective	Disease	Treatment	Active ingredient	Biomarker	Treatment strategy	Result/[price year]	Consideration of test costs/Sensitivity and specificity	Funding
van den Akker-van Marle, M. E./ Gurwitz, D./ Detmar, S. B. et al. (2006) [32]	Four European member states (Germany, Ireland, Netherlands, UK)/societal perspective	Acute lymphoblastic leukaemia (ALL)	n.s.	Mercaptopurine	TPMT	(a) TPMT-genotyping: dosing mercaptopurine according to TPMT activity (wildtype (normal), intermediate, or deficient) (b) no TPMT-testing: standard doses	ICER (a) vs. (b): €4800 ($5702) per LYG [price year 2004]	yes/yes	European Commissions: European Science and Technology Observatory network (ESTO)
Behl A. S./Goddard K. A. B./Flottemesch T. J. et al. (2012) [33]	USA/perspective n. s.	Metastatic colorectal cancer (mCRC)	Second-line therapy (after failed chemotherapy)	Cetuximab vs. BSC	KRAS + (BRAF)	(a) No KRAS-Testing and no anti-EGFR therapy (cetuximab): all patients receive BSC (b) KRAS and BRAF-mutation screening: Patients without KRAS and BRAF mutation receive anti-EGFR therapy (cetuximab) (c) KRAS mutation screening: Patients without KRAS mutation receive Cetuximab (d) no KRAS testing: anti-EGFR therapy (Cetuximab)	ICER (b) vs (a): $648,396 pro LYS ICER (b) vs. (d): most cost effective strategy (significantly lower costs at marginally less benefit) ICER (c) vs. (d): is dominated by (b) vs. (d) [price year 2010]	yes/no	National Cancer Institute at the National Institutes of Health
Blank, P. R./Schwenkglenks, M./Moch, H. et al. (2010) [34]	Switzerland/ health care system	Breast cancer (early stage)	Second-line therapy (after adjuvant or neoadjuvant chemotherapy)	Trastuzumab	HER2	(a) IHC-/ FISH-Test: all patients**: reference strategy** (no Trastuzumab) (b) IHC-test and subsequent FISH-test for IHC2+ patients: trastuzumab treatment for FISH+ or IHC3+ patients; standard therapy for all other patients (c) FISH-Test: trastuzumab treatment for FISH+ patients; standard therapy for all other patients (d) IHC-Test: trastuzumab treatment for IHC 2+ and IHC3+ patients; standard therapy for all other patients (e) IHC-test and FISH-test (parallel): trastuzumab treatment for IHC2+ and IHC3+ and/or FISH+ patients; standard therapy for all other patients (f) No IHC-test/FISH-Test: all patients receive trastuzumab	ICER (c) vs. (a): €12,245 (US$15,676) per QALY ICER (f) vs. (e): €13,456,577 (US$17,226,646) per QALY ICER (e) vs. (c): €400,154 (US$512,263) per QALY ICER (b) vs (a): dominated (higher costs and less effective) (e) vs. (f) is dominated by (c) vs. (f) (d) is dominated by (c): less effective and more expensive (b) is extendedly dominated by (c): less expensive but also less cost-effective [price year n. s.*]	yes/yes	ETH Zurich Foundation; Competence Center for Systems Physiology and Metabolic Diseases (CC-SPMD)
Blank, P. R./Moch, H./ Szucs, T. D. et al. (2011) [35]	Switzerland/ health system	Metastatic colorectal cancer (mCRC)	Second-line therapy (after failed chemotherapy)	Cetuximab + BSC vs. BSC	KRAS + (BRAF)	(a) no KRAS-Test and no treatment with cetuximab: all patients receive BSC (b) KRAS Test and a subsequent BRAF Test: KRAS and BRAF wild-type tumour patients receive cetuximab + BSC; patients with a mutation of KRAS and/or BRAF gene receive BSC (c) KRAS Test: KRAS wild-type tumour patients receive cetuximab + BSC; patients with a mutation of KRAS gene receive BSC (d) No KRAS-Test: all patients receive cetuximab + BSC	ICER (b) vs. (a): €62,653 (US$83,279) pro QALY ICER (c) vs. (b): €313,537(US$416,755) pro QALY ICER (d) vs. (c): €314,588 (US$418,152) pro QALY [price year n. s.*]	yes/yes	ETH Zurich Foundation; Competence Center for Systems Physiology and Metabolic Diseases (CC-SPMD)
Carlson, J. J./Garrison, L. P./Ramsey, S. D. et al. (2009) [36]	USA/societal perspective	Advanced non-small cell lung cancer (NSCLC)	Second-line therapy (after failed chemotherapy)	Erlotinib vs. docetaxel	EGFR	(a) EGFR protein expression test: high protein expression (positive) = erlotinib until progression; low protein expression (negative)= docetaxel until progression (IHC) (b) EGFR gene copy test: high gene copy number (positive) = erlotinib until progression; low gene copy number (negative)= docetaxel until progression (GC) (c) no EGFR-Test: erlotinib until progression	ICER (b) vs. (c): US$162,018 per QALY ICER (a) vs. (c): US$179,612 per QALY ICER (b) vs. (a): dominant (ICER of (b) vs. (c) is better than ICER of (a) vs. (c)) [price year 2006]	yes/no	The author was supported in part by a pre-doctoral Fellowship in Health outcomes from PhRMA Foundation

Dong, D./Sung, C./Finkelstein, E. A. (2012) [37]	Asia/perspective n. s.	Epilepsy	First-line therapy	Carbamazepine (CBZ) vs. valproate (VPA)	HLA-B*1502	(a) no HLA-B*1502-Test: all patients receive CBZ/phenytoin (PHT) (b) HLA-B*1502-Test: negative test result = patients receive CBZ/PHT; positive test result = patients receive VPA (c) no HLA-B*1502-testing: all patients receive VPA	ICER (b) vs. (a): US$29,750 per QALY ICER (c) vs. (b): is dominated (higher costs and same efficacy) ICER (b) vs. (a) for 3 major ethnical populations in Singapore: Singapore Chinese: US$37,030 pro QALY Singapore Malays: US$7930 pro QALY Singapore Indians: US$136,630 pro QALY [price year 2010]	yes/yes	Duke-NUS Graduate Medical School
Donnan, J. R./Ungar, W. J./Mathews, M. et al. (2011) [38]	Canada/health care system	Acute lymphoblastic leukaemia (ALL)	n.s.	Mercaptopurine	TPMT	(a) genotypic TPMT-test: dosing mercaptopurine accordingly TPMT activity; TPMT deficiency: dose reducing; no TPMT deficiency: weight-based dosing (b) enzymatic-TPMT-test: dosing mercaptopurine accordingly TPMT activity- TPMT deficiency: dose reducing; no TPMT deficiency: weight-based dosing (c) no testing: weight-based dosing mercaptopurine (standard of care)	(a) total expected costs per patient CAD-$1090 (US$883), expected survival 2.9997 months (b) total expected costs per patient CAD-$1020 (US$826), expected survival 2.9997 months (c) total expected costs per patient CAD-$654 (US$530), expected survival 2.9997 months [price year 2008]	yes/yes	Atlantic Canada Opportunities Agency, the provincial government of Newfoundland and Labrador
Dubinsky, M. C./Reyes, E./Ofman, J. et al. (2005) [39]	Country n. s. /Third-party payer perspective	Inflammatory bowel disease (IBD)	First-line therapy	Azathioprine (AZA)	TPMT	(a) Community care: therapy started on lowest AZA dose threshold of 50 mg; AZA dose could increase to 100 mg AZA, if a patient did not respond clinically at 3 months; After 6 months, patients responding to the 100 mg dose AZA continued current treatment. (b) TPMT screening: AZA dose according to TPMT-genotype: initial doses by TPMT wild-type (normal) = 100 mg AZA; TPMT intermediate = 50 mg AZA; TPMT deficient = no AZA (patients receive MTX (25 mg) (c) TPMT screening and metabolite monitoring: similar to TPMT screening; initial dosing depends on patients´ TPMT genotype: initial dosing by TPMT wild-type (normal) = 100 mg AZA; TPMT intermediate = 50 mg AZA; TPMT deficient = no AZA (patients receive MTX therapy (25 mg); After 4 weeks AZA dose could be adjusted according to patients´ metabolite level (d) Metabolite monitoring: Initial dose at 50 mg AZA; AZA dose could be adjusted according to patients´ metabolite level	(a) is dominated by (b), (c) and (d): higher costs and longer time to reach sustained response (c) vs. (b): higher costs (US$5877 *vs.* US$3681) and faster time to reach sustained response (19.10 *vs.* 18.96 weeks) (no ICER is reported) (d) vs. (c): higher costs (US$6441 *vs.* US$5877) and faster time to reach sustained response (18.66 *vs.* 18.96 weeks) (no ICER is reported) [price year 2004]	yes/no	n. s.
Elkin, E. B./Weinstein, M. C./Winer, E. P. et al. (2004) [40]	USA/societal perspective	Metastatic breast cancer	First-line therapy	Trastuzumab + chemotherapy vs. chemotherapy	HER2	(a) no IHC-/FISH-Test: chemotherapy alone (b) IHC-Test: trastuzumab and chemotherapy for IHC +3 patients; for all others chemotherapy alone (c) IHC-Test and confirmatory FISH-test for patients with +2 und +3: trastuzumab + chemotherapy for FISH+ patients; for all others chemotherapy alone (d) IHC-Test and confirmatory FISH-Test for patients with IHC +2; trastuzumab + chemotherapy for FISH+ or IHC +3 patients; for all others chemotherapy alone (e) IHC: trastuzumab + chemotherapy for IHC +2 und +3 patients; for all others chemotherapy alone (f) FISH-Test: trastuzumab + chemotherapy for FISH+ patients; for all others chemotherapy alone (g) no IHC-/ FISH-Test: trastuzumab + chemotherapy for all	ICER (b) *vs.* (c): less effective (ruled out by extended dominance) ICER (d) *vs.* (c): dominated (more costly + equally effective) ICER (g) *vs.* (f): dominated (higher costs + same effectiveness) ICER (e) *vs.* (g): dominated (less effective + more expensive ICER (c) *vs.* (a): US$125,100 pro QALY ICER (f) *vs.* (c): US$145,400 pro QALY [price year 2002]	yes/yes	National Library of Medicine Research Training Program in Medical Informatics

Hagaman, J. T./Kinder, B. W./Eckman, M. H. (2010) [22]	USA/perspective n. s.	Idiopathic pulmonary fibrosis (IPF)	n.s.	Azathioprine (AZA) in combination with N-acetylcysteine and steroids vs. conservative therapy (no AZA)	TPMT	(a) TPMT-Test: Dosage of AZA according TPMT-activity: normal TPMT activity: standard doses; TPMT intermediate (reduced TPMT activity): reduced doses; TPMT deficient (absent TPMT-activity): conservative therapy without AZA (b) no TPMT-Test: AZA (c) conservative therapy	ICER (a) vs. (c): US$49,156 per QALY ICER (a) vs. (b): US$29,663 per QALY [price year 2007]	yes/no	n. s.
Hall, P. S./McCabe, C./Stein, R. C. et al. (2012) [41]	UK/NHS	Early-stage lymph node-positive breast cancer	First-line therapy	Tamoxifen + chemotherapy vs. tamoxifen	HOXB13-IL17BR	(a) Test of recurrence (Oncotype DX): low recurrence score (RS ≤ 18): no chemotherapy, only tamoxifen; high recurrence score (RS > 18): chemotherapy + tamoxifen (b) standard of care: chemotherapy + tamoxifen	ICER (a) *vs.* (b): £5529 (US$8852)** per QALY (starting age of the patient cohort was 60 years) [price year 2011]	yes/no	No external funding
Hughes, D. A./Vilar, F. J./Ward, C. C. et al. (2004) [42]	UK/NHS	HIV/AIDS	First-line therapy	Abacavir-containing combination therapy vs. alternative highly active antiretroviral therapy (HAART) without abacavir	HLA-B*5701	(a) HLA-B*5701-Test: negative test result = Abacavir-containing regimens (by a HSR: further treatment with alternative HAART); positive test result = alternative HAART (b) no HLA-B*5701-Test: Abacavir-containing regimens (by a HSR: further treatment with alternative HAART)	(a) *vs.* (b): ranged from dominant strategy (less expensive + more effective) up to €22,811 (US$26,714) per avoid HSR (population of 1000 patients) (depending on the costs of respective alternative HAART: low cost = ICER dominant; high cost = ICER up to €22,811 (US$26,714) per avoid HSR) [price year 2002]	yes/yes	n. s.
Kapoor, R./Martinez-Vega, R./Dong, D. et al. (2015) [43]	Singapore/healthcare system	HIV infection (early and late stage)	First-line therapy	First-line ABC-based ART substituted with tenofovir-based ART as second-line in the event of side effects vs. first-line tenofovir-based ART substituted with ABC-based ART in the event of side effects	HLA-B*5701	**Tenofovir and abacavir can be prescribed as first-line treatment** <u>Early Stage</u> (a) No HLA-B*5701-testing: ABC as first line (Chinese (a1); Malays (a2); Indians (a3) (b) HLA-B*5701: ABC as first-line Chinese (b1); Malays (b2); Indians (b3) (c) HLA-B*5701-testing before ABC: Tenofovir as first line Chinese (c1); Malays (c2); Indians (c3) (d) No HLA-B*5701 done before ABC: Tenofovir as first-line [Chinese (d1); Malays (d2); Indians (d3)] <u>Late stage:</u> (e) No HLA-B*5701-testing: ABC as first line Chinese (e1); Malays (e2); Indians (e3) (f) HLA-B*5701: ABC as first-line Chinese (f1); Malays (f2); Indians (f3) (g) HLA-B*5701-testing before ABC: tenofovir as first line Chinese (g1); Malays (g2); Indians (g3) (h) No HLA-B*5701 done before ABC: tenofovir as first-line Chinese (h1); Malays (h2); Indians (h3) **Patients who are contraindicated to tenofovir** <u>Early stage</u> (i) No genetic testing Chinese (i1); Malays (i2); Indians (i3) (j) HLA-B*5701-testing Chinese (j1); Malays (j2); Indians (j3) <u>Late stage</u> (k) No genetic testing Chinese (k1); Malays (k2); Indians (k3) (l) HLA-B*5701-testing Chinese (l1); Malays (l2); Indians (l3)	ICER (b1) *vs.* (a1): US$415,845/QALY ICER (b2) *vs.* (a2): US$318,029/QALY ICER (b3) *vs.* (a3): US$208,231/QALY ICER (f1) *vs.* (e1): US$926,938/QALY ICER (f2) *vs.* (e2): US$624,297/QALY ICER (f3) *vs.* (e3): US$284,598/QALY ICER (j1) *vs.* (i1): US$252,350/QALY ICER (j2) *vs.* (i2): US$154,490/QALY ICER (j3) *vs.* (i3): US$44,649/QALY ICER (l1) *vs.* (k1): US$757,270/QALY ICER (l2) *vs.* (k2): US$454,223/QALY ICER (l3) *vs.* (k3): US$114,068/QALY	yes/yes	n. s.
Kauf, T. L./Farkouh, R. A./Earnshaw, S. R. et al. (2010) [44]	USA/health care system	HIV/AIDS	First-line therapy	Abacavir and lamivudine + efavirenz (fixed dosed regimen) vs. alternative high active antiretroviral therapy (HAART) with tenofovir+emtricitabine+efavirenz (fixed dosed)	HLA-B*5701	(a) HLA-B*5701-Test: negative test result = abacavir-containing regimens (by a HSR: further treatment with alternative HAART); positive test result = alternative HAART (b) no HLA-B*5701-Test: abacavir-containing regimens (by a HSR: further treatment with alternative HAART)	(a) *vs.* (b): US$328 per avoid HSR [price year 2007]	yes/yes	GlaxoSmithKline, Inc. (Research Triangle Park, NC, USA)
de Lima Lopes, G./Segel, J. E./Tan, D. S. et al. (2012) [45]	Asia/perspective n. s.	Non-small cell lung cancer (NSCLC)	First- or second-line therapy	Gefitinib vs. chemotherapy	EGFR	(a) no EGFR-testing: chemotherapy as first-line therapy, subsequent treatment with gefitinib as second-line treatment (standard therapy) (b) EGFR-testing: patients with activating EGFR-mutation receive gefitinib as first-line therapy and chemotherapy as second-line therapy; patients without mutation receive chemotherapy as first-line therapy and BSC as second-line therapy	ICER (b) *vs.* (a): dominant (less expensive and more effective) [price year 2010]	yes/no	AstraZeneca (Singapore) Pte Ltd (biopharmaceutical company)

Lyman, G. H./Cosler, L. E./Kuderer, N. M. et al. (2007) [46]	USA/societal perspective	Early-stage breast cancer	First-line therapy	Tamoxifen + chemotherapy vs. tamoxifen	HOXB13-IL17BR	(a) 21-gene RT-PCR assay: low risk patients (recurrence score <18): tamoxifen alone; intermediate (recurrence score 18-30) and high-risk patients (recurrence score ≥ 31) receive chemotherapy and tamoxifen. (b) no test: chemotherapy + tamoxifen (c) no test: tamoxifen	ICER (a) *vs.* (c): US$1944 per LYS ICER (a) *vs.* (b): US$3385 per LYS [price year n.s.]	yes/no	Genomic Health; Amgen
Marra, C. A./Esdaile, J. M./Anis, A. H. (2002) [47]	Canada/payer perspective	Rheumatological conditions (rheumatoid arthritis and systemic lupus erythematosus)	n.s.	Azathioprine (AZA)	TPMT	(a) genotype TPMT-Test: AZA dosing according to genotype/TPMT-activity = TPMT homozygous wild type (normal TPMT-activity): target dose of 2.0-2.5 mg/kg/day; TPMT heterozygous (reduced TPMT-activity): target dose 1.0 mg/kg/ day; TPMT homozygous mutant (deficient of TPMT-activity): target dose 0.25 mg/kg/day (b) no TPMT-Test: normal dosing	(a) dominates (b) (more effective and less costly) [price year 1999]	yes/yes	Canadian Arthritis Network (a Canadian Network of Centres of Excellence)
Nieves Calatrava, D./De la Calle-Martin, O./Iribarren-Loyarte, J.(2009) [48]	Spain/National Health System	HIV infection	First-line Therapy	Abacavir (ABC)	HLA-B*5701	(a)HLA-B*5701-Test: positive test result: patients receive a HAART regimen without ABC; patients with a negative test result receive a HAART regimen with ABC (b) No HLA-B*5701-Test: all patients receive ABC	Incremental cost: (a) *vs.* (b) €630.16 (US$807) per HSR avoid [price year 2008]	yes/yes	GlaxoSmithKline
Oh, K.-T./Anis, A. H./ Bae, S.-C. (2004) [49]	Korea/ societal perspective	Rheumatoid arthritis and systemic lupus erythematosus	Second-line therapy	Azathioprine (AZA)	TPMT	(a) genotypic TPMT-Test: AZA dosing according to genotype/TPMT-activity: • TPMT wild type (high activity): Initial dosage 1 mg/kg, dose increment began at 4 weeks; further increment: 0.5 mg/kg steps at 4-week-intervals (target daily dose: 2.5 mg/kg); • TPMT intermediary/heterozygous mutant type(reduced activity): Initial dosage: 0.5 mg/kg, dose increment began at 4 weeks, further increment: 0.5 mg/kg steps at 4-week-intervals (target daily dose: 1 mg/kg); • TPMT deficient/ homozygous mutant type (low or no activity): Initial dosage: 0.25 mg/kg, no increment. (b)no TPMT-Test: conventional weight-based dosing of AZA started at 1 mg/kg daily, dose increase began at 8 weeks in 0.5 mg/kg steps (4-week intervals) up to the target dose of 2.5 mg/kg.	(a) *vs.* (b): dominant (less costly + more effective) [price year 2002]	yes/yes	Korea Health 21 R&D project - Ministry of Health and Welfare (Republic of Korea)
Plumpton, C./Yip, V./Marson, A. et al.(2015) [50]	UK/National Health Service (NHS)	Epilepsy	First-line therapy	Carbamazepine (CBZ)	HLA-A*31:01	(a) No HLA-A*31:01-testing: all patients receive CBZ (b) HLA-A*31:01-Testing: positive test result: patients receive CBZ; negative test result: patients receive lamotrigine	ICER (b) *vs.* (a) per LYG: dominated ICER (b) *vs.* (a) per seizure-free year: dominated ICER (b) *vs.* (a) per cutaneous ADR avoid: £37,314 (US$53,674) ICER (b) *vs.* (a) per QALY gained: £12,808 (US$18,424) [price year 2010-2011***]	yes/no	NIHR Cochrane Programme Grant Scheme 10/4001/18: Clinical and cost effectiveness of interventions for epilepsy in the NHS; and the NIHR Invention for Innovation (i4i) scheme:
Priest, V. L./Begg, E. J./Gardiner, S. J. et al. (2006) [51]	New Zealand/payer´s perspective (the New Zealand government and patients with IBD	Inflammatory bowel disease (IBD)	First-line therapy	Azathioprine (AZA)	TPMT	(a) no TPMT-Test: standard dosage AZA (b) genotypic-TPMT-Test: dosage of AZA according to TPMT-activity (c) phenotypic-TPMT-Test: dosage of AZA according to TPMT-activity	(a) is dominated by (b) and (c) (c) *vs.* (b): dominant (less costly and more effective) [price year 2004]	yes/yes	No external funding
Rattanaviopapong, W./Koopitakkajorn, N./Mahasirimongkol, S. et al. (2013) [52]	Thailand/societal perspective	Epilepsy and neuropathic pain	First-line therapy	Carbamazepine (CBZ)	HLA-B*15:02	(a) No HLA-B*15:02-Screening: Patients receive CBZ (b) HLA-B*15:02-Screening for all patients: patients with a positive test result receive the alternative drugs; negative tested patients receive CBZ (c) No HLA-B*15:02-Screening: all patients receive an alternative drug treatment	<u>Epilepsy:</u> ICER (b) *vs.* (a): 220,000 THB (US$7066) per QALY ICER (c) *vs.* (a): 32,522,000 THB (US$1,035,073) per QALY <u>neuropathic pain</u> ICER (b) *vs.* (a): 130,000 THB (US$4137) per QALY gained ICER (c) *vs.* (b): 35,877,000 THB (US$1,141,852) per QALY gained [price year 2011]	yes/yes	n. s.

Schackman, B. R./Scott, C. A./Walensky, R. P. et al. (2008) [53]	USA/perspective n. s.	HIV/AIDS	First-line therapy	Abacavir-based treatment vs. tenofovir-based treatment	HLA-B*5701	(a) HLA-B*5701-testing: negative test result: abacavir-based treatment (abacavir + lamivudine + efavirenz); positive test result: tenofovir-based treatment (b) No HLA-B*5701-testing: abacavir-based therapy (abacavir + lamivudine + efavirenz); occurrence of HSR: further treatment with tenofovir-based treatment (c)No HLA-B*5701-testing: tenofovir-based therapy (renofovir + emtricitabine + efavirenz); occurrence of nephrotoxicity: substituting abacavir and lamivudine	ICER (a) *vs.* (b): US$36,700 pro QALY ICER (c) *vs.* (b): is dominated (higher costs + less effective) [price year 2006]	yes/no	National Institute of Allergy and Infectious Diseases; National Institute on Drug Abuse
Shiroiwa, T./Motoo, Y./Tsutani, K. (2010) [54]	Japan/health care payer	Metastatic colorectal cancer (mCRC)	First-line therapy	Cetuximab vs. BSC	KRAS	(a) KRAS testing: patients with KRAS wild-type receive cetuximab; patients with KRAS-mutation receive BSC (b) no KRAS-testing - all patients receive cetuximab (c) no KRAS-testing - all patients receive BSC	ICER (b) *vs.* (c): US$160,000 pro LYG; US$230,000 pro QALY ICER (a) *vs.* (c): US$120,000 pro LYG; US$180,000 pro QALY ICER (a) *vs.* (b): dominant (lower cost with the same or better outcome) [price year 2010]	yes/no	Roche Diagnostics KK.
Thompson, A.J./Newman W.G/Elliott, R. A. et al. (2014) [12]	UK/health service perspective	Autoimmune diseases	n.s.	Azathioprine (AZA)	TPMT	(a)No TMPT- genotyping (current practice): • TMPT-wild type (normal activity): starting dose: 0.86 +/- 0.53 mg AZA; Maintenance dose at 4 months: 1.74 +/-0.50 mg AZA; • TMPT-heterozygous (low activity): starting dose: 0.93 +/- 0.64 mg AZA; Maintenance dose at 4 months: 1.62 +/-0.56 mg AZA (b) TPMT genotyping: • TMPT-wild type (normal activity): starting dose: 0.92 +/- 0.60 mg/kg/d AZA; Maintenance dose at 4 months: 1.62 +/-0.55 mg/kg/d AZA • TMPT-heterozygous (low activity): starting dose: 0.61 +/- 0.33 mg/kg/d AZA; Maintenance dose at 4 months: 1.80 +/-0.89 mg/kg/d AZA	Incremental costs (adjusted) for TPMT-genotyping: (b) *vs.* (a): £421.06 (US$625) Incremental QALY for TPMT-genotyping: (b) *vs.* (a): -0.008 Incremental net benefit (b) *vs.* (a): £256.89 ($381) [price year 2009-2010***]	yes/no	TARGET-Study: The Department of Health UK; A.J. Thompson: NIHR School for Primary Research; Prof. Payne-Research Councils UK (partly)
Vijayaraghavan, A./Efrusy, M. B./Göke, B. et al. (2012) [55]	USA and Germany/health care payer perspective	Advanced metastatic colorectal cancer (mCRC)	Second-line therapy (after failed prior chemotherapy)	Cetuximab panitumumab Combination therapy (US: cetuximab+irinotecan; Germany: cetuximab+FOLFIRI) Combination therapy (US: cetuximab+irinotecan; Germany: cetuximab+FOLFIRI) vs. irinotecan (US) or FOLFIRI (Germany)	KRAS	(a) no KRAS-testing: panitumumab (b) KRAS-testing: panitumumab (c) no KRAS-testing: cetuximab (d) KRAS-testing: cetuximab (e) no KRAS-testing: combination therapy: USA: cetuximab + irinotecan, Germany: cetuximab + FOLFIRI (f) KRAS-testing: combination therapy: USA: cetuximab + irinotecan, Germany: cetuximab + FOLFIRI; (Assumption: patients with KRAS mutation will not receive chemotherapy) (g) KRAS-testing: combination therapy: USA: cetuximab + irinotecan, Germany: cetuximab + FOLFIRI; patients with KRAS mutation (wild type) receive irinotecan (US) and FOLFIRI (Germany)	ICER (b) *vs.* (a): dominant (lower costs + same effectiveness) ICER (d) *vs.* (c): dominant (lower costs + same effectiveness (f) *vs.* (e): less expensive + less effective = no ICER stated (g) *vs.* (e): lower costs + same effectiveness, no ICER stated ICER (g) *vs.* (f): US$35,539 pro LYS [price year 2009]	yes/yes	Roche Molecular Systems, Inc., United States (Roche)
Winter, J./Walker, A./Shapiro, D. et al. (2004) [56]	UK/perspective n. s.	Inflammatory bowel disease (IBD)	Second-line therapy	Azathioprine (AZA) vs. alternative treatment	TPMT	(a) TMPT-Test: AZA dosing according to genotype/TPMT-activity: homozygote does not receive AZA, heterozygotes receive a reduced dose AZA (b) no TMPT-Test: all patients receive AZA	(a) vs. (b): £487 (US$776) per LYS (for a 30 year old patient) or £951 (US$1515) per LYS (for a 60 year old patient) [price year n. s.*]	yes/yes	n. s.

Abbreviations: ICER: incremental cost-effectiveness ratio; LYS: life-year saved; LYG: life-year gained; QALY: quality adjusted life years; n.s.: not stated; HSR: hypersensitivity reaction; ADR: adverse drug reaction; THB: Thai Baht; CAD: Canadian Dollars

*As price year, the second year prior to the publication year, was assumed.

** Not calculated by the authors

*** An average exchange rate of these two price years was calculated.

Modul 6

Genomanalysen als Informationseingriff: Ethische, juristische und ökonomische Analysen zum prädiktiven Potential der Genomsequenzierung

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2016

Modul 7

Which attributes of whole genome sequencing tests are most important to the general population? Results from a German preference study

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ORIGINAL RESEARCH

Which attributes of whole genome sequencing tests are most important to the general population? Results from a German preference study

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Objective: The aim of this study was to identify the preferences for whole genome sequencing (WGS) tests without genetic counseling.

Methods: A discrete choice experiment was conducted where participants chose between two hypothetical alternatives consisting of the following attributes: test accuracy, test costs, identified diseases, probability of disease occurrence, and data access. People from the general German population aged ≥18 years were eligible to participate in the survey. We estimated generalized linear mixed effects models, latent class mixed-logit models, and the marginal willingness to pay.

Results: Three hundred and one participants were included in the final analysis. Overall, the most favored WGS testing attributes were 95% test accuracy, report of severe hereditary diseases and 40% probability of disease development, test costs of €1,000, and access to test results for researchers. Subgroup analysis, however, showed differences in these preferences between males and females. For example, males preferred reporting of results at a 10% probability of disease development and females preferred reporting of results at a 40% probability. The test cost, participant's educational level, and access to data influenced the willingness to participate in WGS testing in reality.

Conclusion: The German general population was aware of the importance of genetic research and preferred to provide their own genetic data for researchers. However, among others, the reporting of results with a comparatively relatively low probability of disease development at a level of 40%, and the test accuracy of 95% had a high preference. This shows that the results and consequences of WGS testing without genetic counseling are hard to assess for individuals. Therefore, WGS testing should be supported by qualified genetic counseling, where the attributes and consequences are explained.

Keywords: whole genome sequencing, discrete choice experiment, genetic testing, preferences, willingness to pay, latent class model

Introduction

In the past 10 years, significant progress has been achieved in the fields of genomics and genetics.[1] The usage of genetic information has steadily increased in medical research, diagnosis, and therapy. Essential drivers for this development are as follows: 1) technological progress such as next-generation sequencing (NGS) technologies, 2) the reduction in costs of sequencing,[2] 3) growth in population and clinical-based biobanks,[3] and 4) the increasing knowledge of genotype–phenotype correlations based on genome-wide association studies (GWAS).[4]

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Genetic information is essential for personalized medicine. This knowledge enables preventive health care management as well as the administration of personalized and targeted therapies based on an individual's genetic characterization.[5] The scope of analysis (gene, panel, exome, or whole genome sequencing [WGS]) and the amount of genetic data vary with the aim of the investigation. WGS provides an opportunity to identify almost all disease-causing variants.[6] For this reason, WGS seems to be the most appropriate method for comprehensive predictive analysis.

In recent years, the suitability of WGS as a screening tool has been discussed, especially in newborn[7] or population-based screening.[8] Notwithstanding the economic (eg, clinical utility),[9] ethical, and legal debates (eg, information of self-determination),[10] the detection of rare and/or highly penetrant diseases before the onset of disease may have considerable advantages. For example, previous surveys indicated that early diagnosis of cystic fibrosis[11] or Lynch syndrome[12] is beneficial for treatment, and the knowledge of predispositions to oncological and cardiovascular diseases can be useful for prevention. Knowledge of a BRCA I/BRCA II mutation allows the development of a prevention strategy including regular checkups and mastectomy.[13]

Several studies showed that people are interested in genetic testing.[14–16] They want to take a proactive role in preventive health care management for themselves as well as for their family members.[17] However, WGS testing aimed at primary prevention without a suspected disease is generally not covered by health insurance plans (eg, in Germany). Genetic analysis distributed via the Internet is a less expensive alternative than the conventional market.[18] Such offers often lack qualified genetic counseling,[19] which is essential for an informed decision regarding WGS testing. Qualified genetic counseling supports complex decision-making with regard to the following questions: Do the results affect my family members? Who has access to my genetic information? What is the potential for genetic discrimination (eg, in terms of insurability)? Am I willing to pay for the testing out-off-pocket? Do I want to know the probability of developing all diseases or only the probability of developing treatable diseases? How sensitive is the test?

For the purpose of identifying relevant attributes of online WGS testing, we conducted a discrete choice experiment (DCE) to evaluate the preferences of the general population. We investigated the people's preference estimates without prior qualified genetic counseling. We analyzed 1) the preferences of our study population and subgroup effects (eg, sociographic characteristics, genetic predisposition, and desire for children), 2) the willingness to pay of these subgroups, and 3) factors influencing the willingness to take part in WGS tests.

Methods

DCE

We conducted a DCE to measure the preferences for WGS testing. A DCE is a de-compositional approach to the measurement of stated preferences. Participants have to choose between hypothetical alternatives. One alternative consists of several attributes with varying levels.[20] The attributes are characteristics of the alternatives that are specified by their levels for each alternative.

Attributes and levels

First, we conducted a literature search to achieve a comprehensive overview of the available attributes of WGS. However, no literature focusing on preferences for WGS attributes could be identified. Hence, we adopted relevant attributes from actual discussions and literature focused on genetic analysis. The final relevant attributes for the DCE were "test accuracy",[21] "test cost",[22] report of results[23–25] (divided into "identified diseases" and "probability of occurrence"), and "access to data".[26] The range of levels was also determined by specific discussion points or based on the literature on the subject. Finally, attributes and levels were discussed with experts. To improve the validity and reliability of each item, a pretest of the questionnaire was conducted with 11 people. Table 1 illustrates the attributes and their corresponding levels. The attributes and levels are explained using colloquial language and icons, and they were adjusted after the pretest.

Data collection and recruitment

People from the German general population aged ≥18 years were eligible to participate in the survey. It was an online survey via Facebook and Xing that was conducted from June to August 2016, as well as by direct (and random) approach of passersby with a paper–pencil questionnaire at the main railway station in the city of Hannover (northwestern Germany). We used a simple random sampling strategy and did not select participants according to age and sociodemographic or economic status. We obtained study approval from the ethics committee of Hannover Medical School (Re No 3325-20016) prior to the start of the survey. To take part in the study, participants had to give written informed consent.

Table 1 Overview of attributes with the corresponding levels

Attribute	Description in the questionnaire	Level 1	Level 2	Level 3	Level 4
Accuracy (sensitivity)	Test accuracy describes the proportion of persons with an identified genetic mutation that actually have this mutation For example, a level of 90% means that 90 of the 100 people really have the risk to develop a certain disease. In contrast, in 10 of the 100 people, a disease risk is identified because of inaccuracy of the test, although they do not have this risk You can choose between different tests with different accuracy values	90% 	95% 	99% 	
Identified diseases	You can choose about the test results you want to be informed You can choose the test results that you want to be informed about. You have the choice between reporting of all test results, only treatable diseases (preventive and therapeutic treatments), and serious hereditary diseases In case of serious hereditary diseases, it is assumed that these are inherited with a high probability and are characterized by a serious disease progression	All diseases	Treatable disease	Serious hereditary disease	
Test costs	A WGS is an innovative, diagnostic instrument and currently associated with high execution costs. You should decide how much money you are willing to pay for this comprehensive genetic analysis	€500 	€1,000 	€1,500 	
Probability of occurrence	The results of a WGS determine the risk of being affected by a specific disease. A genetic mutation enables statements about the probability of developing different diseases. You can decide which probability of developing a disease you want to be informed	10%	40%	70%	
Access to data	WGS is associated with a large amount of personal data. You can decide who can get access to your test results in addition to you and your treating physician For example, you can make your genetic data accessible to researchers and thus contribute to medical research	No one else 	Insurer 	Researcher 	Insurer and researcher 

Abbreviation: WGS, whole genome sequencing.

Questionnaire

The final questionnaire consisted of three sections. The first part was the DCE choice sets. In total, the attributes and levels resulted in $3^4 \times 4^1 = 324$ possible combinations (four attributes with three levels and one attribute with four levels).[20] To generate feasible choice sets of the DCE, a *D*-efficient fractional factorial design (reduced design) was created using the R statistical program. The best *D*-efficiency occurred for 18 choice sets. To avoid overstraining of the participants, we divided the 18 choice sets into two questionnaires (blocking). Therefore, participants answered nine DCE decisions with two alternatives (called Test 1 and Test 2) each. Additionally, we asked whether the participant would carry out the chosen test in reality (refer the example of the choice in Figure 1). The second part focused on sociodemographic questions, such as sex, age, education, occupation, monthly net income, and insurance company (statutory or private). The third part included questions about overall health status, prevention behavior, hereditary diseases, and desire for children.

Data analysis

Following survey completion, we cleaned the data set and determined descriptive statistics for the variables (median, standard deviation [SD], and percentages). We tested the potential independent variables for multicollinearity to reduce the bias of the results. In the multivariate analyses, we applied generalized linear mixed-effects models (GLMMs) and latent class mixed logit models (LCMLMs) to identify systematic or group differences for the participants' WGS preferences. The choice of an alternative between two hypothetical WGS

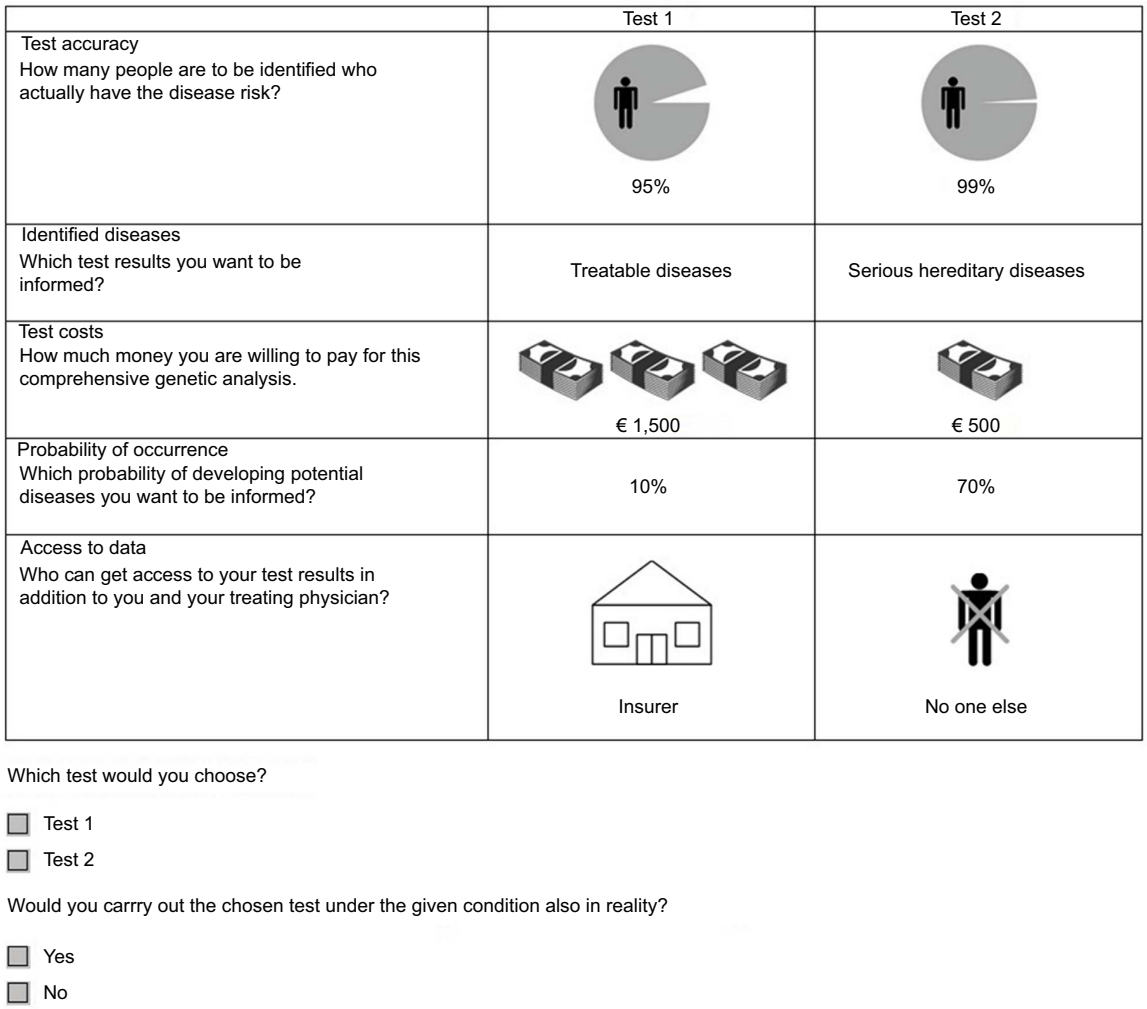


Figure 1 Example of a choice set.
Notes: Explanation for the example choice set: The participant could choose between test 1 and test 2. Test 1 is characterized by a lower test accuracy (95%), with the reporting of treatable results at a 10% probability of disease occurrence as well as higher cost (€1,500), and the access for insurer. Test 2 is designed with a higher accuracy (99%), with the reporting of serious hereditary diseases at a higher probability of disease occurrence (70%) and at lower cost (€500). Furthermore, in test 2, no one else had access to the test results. The participant has to trade-off between a test accuracy of 95 and 99%, the costs of €1,500 and €500, and so on.

tests (choice) was used as the dependent variable, whereas the attributes and levels were the independent variables in all models. In addition, personal characteristics of the participants were used as independent variables, mixed effects (taking into account that personal characteristics influence the response behavior and therefore including subgroup specific "baseline" values [random intercept] or slope adjustments [random slope] for some of the independent variables in addition to the fixed effects), or class-membership effects (for LCMLM). We calculated the average marginal willingness to pay (mWTP) for each attribute by dividing the coefficients for the other attributes by the coefficient of the cost attribute (test costs). Therefore, we used the attributes as metric independent variables in conditional logit models and conducted the mWTP analysis separately for the different classes from the LCMLM analyses. Coefficients of attributes above zero were favored, and negative coefficients were disfavored. The 95% confidence intervals (CIs) are based on the Krinsky and Robb[27] method.

We calculated the GLMM for participants willing to participate in reality (potential users) and the full sample separately, so that any differences between these two groups could be identified. In the GLMM, we used the set ID (identification number of the choice set) as a mixed effect to

inform the model about which of the alternatives formed a set. Finally, we investigated the factors influencing the willingness to participate in genetic testing in reality. Therefore, we applied another GLMM based on the variable "real" as a dependent variable. The random effect used in this model was the person identifier (PersonID) to enable us to investigate influencing participants' characteristics and test characteristics based on the decision. An overview of used variables is provided in Table S1.

We tested different independent variables and mixed effects in the models (Table S2) and chose the model with the best fit for data based on Akaike and Bayesian information criteria. All analyses were conducted with R statistics 3.1.2 and the packages "lme4" (for GLMM), "lcmm" (for LCMLM), and "support.CEs" (for mWTP analyses).

Results

Descriptive statistics

In total, 323 people participated in the study and 301 people could be included in the DCE analyses. All sample characteristics are provided in Table 2. Twenty-two participants had to be excluded because of missing data for all DCE tasks or an age of <18 years. The sample consisted of 69% women, and the median age was 28 years. The educational level was higher compared to that of the general population of Germany,[28] but the average amount of income was similar.[29] Both facts indicated that the proportion of students was higher compared to the general population. The majority (56%) of the participants were in good health.

In a second step, we prepared the data for the multivariate analyses. We found strong correlations between age and employment status, having children and employment status, and age and desire to have a child (refer correlation plot in Figure S1). Therefore, we adapted the models for these correlations due to not using both correlating variables in one model or due to including interaction effects between the correlating variables.

Table 2 Sample description

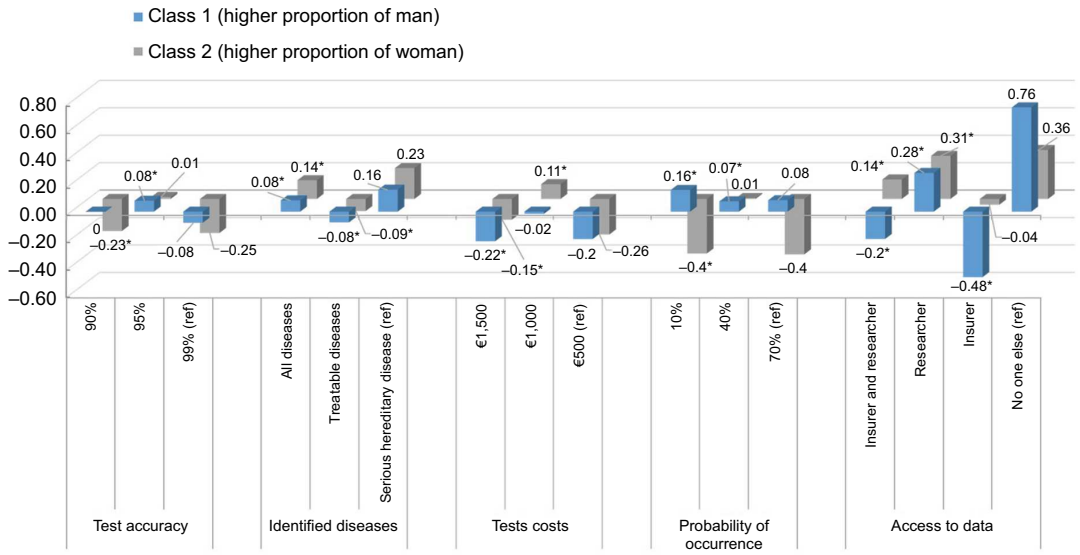
Variable	Occurrence in the sample
Participants (number)	323
With at least one valid DCE task	301
Sex (% women)	69
Age in years (median, SD)	28 (13.86)
Own children (% having at least one child)	41
Desire to have children (%)	
Yes	50
No	39
Unsure	11
Highest level of education (%)	
No graduation	1
Primary school	6
Secondary school	34
High school	24
University	34
Income (%)	
No own income (€)	16
<1,000	27
1,000–<2,000	29
2,000–<3,000	17
3,000–<4,000	6
≥4,000	4
Participation in screening program (%)	
Never	51
Every 10 years	3
Every 5 years	9
Every 2 years	21
1–2 times a year	15
Subjective health status (%)	
Very bad	0
Bad	4
Medium	24
Good	56
Very good	16
Hereditary diseases in the family (% yes)	20
Afraid of hereditary diseases (% yes)	21

Note: Median: average.
Abbreviations: DCE, discrete choice experiment; SD, standard deviation.

Subgroup-specific preferences for WGS tests

In the LCMLM, we identified two classes that differed in regard to their preferences for genetic testing (Figure 2 and Table S3). Class 1 comprised 46.13% (n=137) of the sample. The only significant differentiator between the people in the two classes was their sex. The proportion of women was significantly lower in class 1 than in class 2 (refer the table in Figure 2). The educational level, health status, and income are relevant for the class membership but did not show significant differences between the classes.

In class 1, a higher proportion of men compared to the other classes strongly preferred the restricted "access to data only for themselves" ($\beta_{\text{class 1,access no}}$=0.76, reference level) and disfavored the "access to data for insurer" the most ($\beta_{\text{class 1,access ins}}$=−0.48, $P < 0.001$). They also disfavored any "test costs" where €1,000 had a utility weight of ~0 but was not significant. Class 1 preferred "serious hereditary diseases identified" and a "10% probability of occurrence" ($\beta_{\text{class 1, ser.d}}$=0.16, $\beta_{\text{class 1, 10\% occ}}$=0.16, P<0.001) (Figure 2). In contrast, class 2 disfavored "10% and 70% probability of occurrence" but also preferred "serious hereditary diseases



Graph adjusted for further effects: mixture = –Att_TA + Att_DIS + Att_TC + Att_ACC, random = ~seti, subject= "personID", classmb= ~sex + EDL + INCn + HSn

Class-membership effects	Class 1 (ref = class 2)		
	Coefficient	Standard error	*P*-value
Intercept	1.93	0.94	0.04
Sex (ref = male)	–0.64	0.29	0.03
Educational level	0.09	0.14	0.54
Health status	–0.28	0.19	0.14
Income	–0.09	0.11	0.40

Figure 2 LCMLM for preferences concerning genetic testing – attribute effects.
Note: *Significant values (*P*<0.05).
Abbreviations: EDL, educational level; HSn, health status (numeric); INCn, income (numeric); LCMLM, latent class mixed logit model.

identified". Indeed, the highest preferences occurred for access to data only for themselves and "for researchers" ($\beta_{\text{class 2, access no}}$=0.36, reference level; $\beta_{\text{class 2, access res}}$=0.31, *P*<0.001). Class 2 also preferred "access to data only for insurer and researcher". Class 2 disfavored "90% and 99% test accuracy" and showed a significant positive utility for "€1,000 test costs".

To conclude, men emphasized the importance of access to data only for themselves and favored a test with 95% accuracy also for diseases with a low probability of occurrence. The class with a higher proportion of women favored instead a test that identifies serious hereditary diseases, where test costs on the intermediate level arise, and that enables data access for themselves or researchers.

In addition, we calculated the mWTP for each attribute, separated for class 1 and class 2 from the LCMLM (Table 3). The mWTP showed different starting points for class 1 and class 2 models ($\text{intercept}_{\text{class 1}}$: €786.3 and $\text{intercept}_{\text{class 2}}$: €–1,931.3). From this, it can be concluded that people in class 2 were willing to pay less money for genetic testing than those in class 1. Furthermore, class 2 was willing to pay on average €740 for an increase of one unit (90%–95% or 95%–99%) in test accuracy (CI: €489.5; €1,218.2) and on average €1,500 (€1,071.5; €2,435.5) for diseases with higher probability of occurrence. In contrast, the mWTP was negative for the identified diseases (€–303.7 [€–560.2; €–127.1]) and the access to data (€–383.8 [€–645.3; €–228.7]). Therefore, people were willing to receive monetary compensation for identifying only treatable and hereditary diseases. Class 1 was willing to pay on average less for a higher test accuracy, although the monetary value was still positive (intercept €786–128=€658 for a change from 90% to 95%). In addition, this class showed negatively associated mWTP for identified diseases (€–164.6 [€–289.7; €–45.1]) and the probability of occurrence (€–502.3 [€–707.4; €–356.8]). In contrast, class 1 was willing to pay ~€723 [€561.2; €967.9] more for less access to data.

Table 3 Marginal willingness of classes to pay for test attributes

Attribute	Levels	Class 1: mWTP in € (95% CI)	Class 2: mWTP in € (95% CI)
Intercept		786.3 (308.5; 1,233.9)	–1,931.3 (–3,935.2; –905.2)
Test accuracy	90%–99%	–127.6 (–258.7; –17.9)	737.8 (489.5; 1,218.2)
Identified diseases	All, treatable, hereditary	–164.6 (–289.7; –45.1)	–303.7 (–560.2; –127.1)
Probability of occurrence	10%–70%	–502.3 (–707.4; –356.8)	1,514.5 (1,071.5; 2,435.5)
Access to data	Insurer, researcher and insurer, researcher, no one else	722.9 (561.2; 967.9)	–383.8 (–645.3; –228.7)

Note: Class 1: higher proportion of men; Class 2: higher proportion of women.
Abbreviations: CI, confidence interval; mWTP, marginal willingness to pay.

Analysis of participation in genetic testing

We estimated GLMMs (full sample, potential users) to identify the preferences for genetic testing. The most important attribute level for genetic testing for both subgroups was the "identification of severe hereditary diseases" (Table S4). Therefore, this attribute level is more important for potential users ($\beta_{user,ser.dis.}$=0.88) than for the full sample ($\beta_{full,ser.dis.}$=0.49). However, the most disfavored attribute level for both subgroups was access to data for insurer ($\beta_{full,insur}$=–0.81, $\beta_{user,insur.}$=–0.64, both P<0.001). It is striking that for test accuracy, identified diseases, test costs, and probability of occurrence, the intermediate level gained the highest utility weight in both subgroups. Although the preferences were similar between the subgroups, the full sample preferred "95% test accuracy", €1,000 test costs, and "access to data for researchers" more strongly than the potential user subgroup.

In the last step, we investigated the factors that influenced the willingness of respondents to participate in genetic testing in reality or if they just preferred the chosen alternative hypothetically. The GLMM showed that from the attributes, only test accuracy and access to data were relevant for the decision (Table 4). All costs reduced the willingness to participate in genetic testing; however, €500 was the least disfavored level ($\beta€_{500}$=–0.024). In addition, people were more willing to participate when the access to data would be denied to insurers and researchers. In contrast to previous models, the decision to participate in reality was positively influenced by access to data for researchers and not "only for themselves". Educational level showed a negative association to the participation in genetic testing. In addition, people who would participate in screenings if the social or private health insurance (SHI) subsidized it were more willing to participate in genetic testing ($\beta_{scr\ subs\ SHI}$=1.86, P<0.001). "Employment status", "income", and "fear of genetic diseases" did not show significant results, although the direction of the coefficients was as expected.

Table 4 GLMM fixed-effects results for participation in genetic testing

Variables	Levels	Coefficient	SE	*P*-value
Test costs	€1,500	–0.261	0.100	0.009
	€1,000	–0.237	0.090	0.009
	€500 (ref)	–0.024		
Probability of occurrence	10%	–0.089	0.101	0.375
	40%	–0.012	0.094	0.897
	70% (ref)	–0.077		
Access to data	Insurer and researcher	–0.275	0.118	0.019
	Researcher	0.097	0.106	0.358
	Insurer	–0.349	0.134	0.009
	No one else (ref)	–0.024		
Educational level		–0.693	0.263	0.008
Employment status		–0.858	0.541	0.113
Income		0.338	0.226	0.134
Screening utilization: subsidy by SHI		1.857	0.465	0.000
Afraid of genetic diseases		0.975	0.564	0.084

Notes: Intercept coefficient 1.409; SE 1.231; P 0.252 and random intercept PersonID variance 9.765; standard deviation 3.125.
Abbreviations: GLMM, generalized linear mixed-effects model; SE, standard error; SHI, social or private health insurance.

Main findings

The most preferred test for the overall sample was characterized by the following aspects: 1) the test accuracy of 95%, 2) report of severe hereditary diseases, 3) the test cost of €1,000, 4) report of results for diseases with a probability of occurrence from 40%, and (5) access to genome data for researcher but not for insurers (Table S4). Except for "access to genome data", all intermediate levels achieved the highest utility weights in both the full sample and the sample of potential users (Table S3).

Discussion

In this study, the preferences for WGS testing without qualified genetic counseling were assessed.

The test accuracy of 95%, especially sensitivity in this case, was the most favored level of this attribute. This may show that the participants did not understand (or only partly understood) the underlying concept of test sensitivity and

false-positive results. We expected that the most preferred level would be 99% test accuracy. False-positive findings lead to anxiety and uncertainty for the tested person as well as for their families.[30] This in turn may require an additional diagnostic clarification or leads to an increased treatment demand (eg, psychological counseling). Finally, false-positive results could cause an unnecessary rising cost for the statutory health insurance. Otherwise, the participants may understand the underlying concept but accept the uncertainties to receive other advantages, eg, lower test costs.

The amount of reported results was also an important aspect for the decision regarding WGS tests. This aspect is represented by the probability of occurrence (in this experiment 10%, 40%, or 70%) as well as by the kinds of reported diseases (all disease dispositions, only treatable [potential] disorders, or only severe hereditary diseases). The majority of the participants preferred the reporting of serious hereditary diseases. "All disease dispositions" were not attributed with the highest utility score; this may be in accordance with the aspects of efficiency and evidence. Technological progress and genetic research enables the detection of a majority of diverse gene variants. However, many identified genetic variations are not assigned to phenotypes, or the interaction of the specific gene variants is actually unknown.[31] This may change in the future because of further genomic research, especially through GWAS. So far, there are no therapy options for most of the identified gene variants and diseases. However, the participants preferred 40% "probability of disease occurrence". This may indicate that the general population cannot assess the absolute risks for developing a disease without counseling or the influence on disease development caused by lifestyle changes (e.g., sports, nutrition), or that prevention measures may be assessed as a more important and changeable factor. These preferences could occur because of unawareness about genetic risk factors of the participants, due to lack of qualified counseling, or because of their risk aversion. Another limiting factor could be the three given levels of the probabilities. Since the participants were forced to prefer one of the given levels, the range of the outcomes could also be limited. However, the first explanation is emphasized by the negative effect of educational level on the willingness to participate (Table 4).

Cost reduced the willingness to participate in the WGS testing in reality (Table 4). Accordingly, subsidies by SHI for WGS testing showed a positive effect on the willingness to participate in testing. However, €1,000 received the highest approval in the LCMLM. This may be due to the association between the rising costs and the quality or the knowledge of the "$1,000 genome", which means the often discussed cost reduction of a WGS to $1,000 in recent years.[32] Otherwise, health care systems with little or no out-of-pocket payments for prevention measures could influence the importance of cost attributes for the participants' decisions. However, the participants' income did not influence the class membership and preferences. In the mWTP analyses, we found that the willingness to pay in class 2 (higher proportion of women) was highest for the attribute of probability of disease occurrence, whereas the highest mWTP occurred for access to data in class 1 (higher proportion of men). Furthermore, the direction of mWTP for several attributes was different for these two classes. Thus, the mWTP seemed highly dependent on the examined subgroup. The formation of class 1 (higher proportion of women) and class 2 (higher proportion of men) highlights the differences between males and females. While males preferred restricted access to data only for themselves, females wanted to make their genetic data accessible to research. Secrecy of personal data is seemingly very important to men, while women may want to contribute to genetic research. Further differences arose in reporting of results. Females and males preferred a reporting of results at a 40% and 10% probability of disease occurrence, respectively. Fear of a variety of predictive findings (women) or the desire to know almost all dispositions (men) may be possible explanations for this finding.

In the future, cost reductions will be expected because of the focus on genetic analyses of specific variants. Currently, for example, in the case of presumed heredity of breast cancer, the first-degree-relative risk patients are often tested only for the specific variant (eg, BRCA I and BRCA II).[33] Further improvements in WGS testing could contribute to it becoming the favorable alternative compared to panel or single gene sequencing.

Potential users as well as the full sample rejected the access of test results to insurance agencies. Fear of genetic discrimination, eg, in terms of insurability or direct and/or indirect risk selection, seems to be particularly substantial.[34] However, due to a ban on discrimination and the obligation to contact, this risk is excluded in the statutory health insurance in Germany. In other insurance areas (private health insurance, life insurance, and occupational disability insurance), these data could have a stronger influence on insurability and insurance premium, which may lead to uncertainty and anxiety. Despite the strong regulations, anxiety and fear of data misuse seem to be the sensitive issues. Further research is needed in these areas. However, the DCE results suggested that potential users preferred to give researchers access to

genetic data. Genetic research is a dynamic field, and comprehensive genetic databases are the prerequisite for research. The fear of disease as well as the interest in research and further medical developments may be essential drivers for the preferences in this study. Thus, people have the opportunity to contribute to medical research. With regard to large genome sequencing projects, such as the 100,000 Genomes Project (UK),[35] the Saudi Human Genome Program (Saudi Arabia),[36] and the GoNL (the Netherlands),[37] the German population also showed interest. The reporting of test results could be restricted or completely rejected in qualified WGS testing, eg, to findings of the ACMG-positive list (Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing).[38] Basically, the decision for or against a WGS test in reality depended on the specific design (characteristics level) in 53.26% of the cases. While 26% of the participants rejected a WGS test independent of specific levels, 20.74% of the participants would execute a WGS test independent of the test characteristics in reality.

The possibilities for using genetic testing results in diagnosis and therapy have steadily increased. Therefore, the WGS offers an opportunity to detect a majority of disorders, especially using a predictive approach. However, in Germany, the costs of genetic analyses for patients at risk (eg, first-degree relatives of breast cancer patients) are covered by a variety of health insurance plans, whereas predictive genetic testing for nonpredisposed people is an out-of-pocket expense. Therefore, comprehensive genetic direct-to-consumer (DTC) analysis via the Internet seems to be a less expensive alternative,[18] although DTC options often lack qualified genetic counseling.[19] As we can see from our survey, not all stated preferences are consistent with the qualified recommendations. Therefore, our study results emphasize the importance of genetic counseling. In Germany, human genetic counseling for predictive analysis is obligatory in accordance with the § 10 German Act of Gene Diagnostics (GenDG). Two main results underline the claim for genetic counseling: 1) the chosen test accuracy of 95% and the associated higher risk of false-positive results (in contrast to a test accuracy of 99%) and 2) the selected probability of disease occurrence at a level of 40% for the reporting of results. For a majority of disease dispositions, there are no treatment options at the moment. Therefore, people may be confronted with information on a large number of potential diseases, which will lead to anxiety. Genetic counseling may help to understand what penetrance really means and which consequences of a finding with a probability of 40% occurrence will arise. However, a possible explanation for these preferences might be that people assume that their doctors will receive the WGS test results and help them to understand and interpret their results. The attribute access to data is characterized by the possibility of access to the genetic information by the treating physician. Due to medical secrecy, we excluded the risk and the anxiety of data misuse. A person can decide if they want to share these genetic results with the treating physician, which would be beneficial for understanding. Prior genetic consultations may have an influence on the general decision for the execution and the scope of reporting of the results. However, in the present study, we excluded such a prior consultation to explore the preferences without a qualified genetic counseling (which is partially lacking in a genetic DTC analysis).

One limitation of this experiment is the hypothetical character. The revealed preferences may lead to another distribution of utility weights. Furthermore, the importance of test specificity was neglected. The difference between sensitivity and specificity is difficult for the general population to understand, and therefore, we focused on test sensitivity in the DCE. The representativeness of the sample is also limited. The sample of a primarily online acquisition is mainly characterized by younger and Internet-savvy people. However, we assumed that the topic is most relevant for this group. In the direct approach, we only recruited a small number of participants (n<10), so we could exclude a selection bias. Although we included the relevant test attributes and important sociodemographic characteristics of the study population, further factors (eg, risk aversion) could influence the preferences. The calculations of mWTP should be considered with caution. We treated the level differences as linear, although this is not intuitive. For example, we assumed that the difference from 90% test accuracy to 95% had the same effect as a change from 95% to 99% in mWTP. However, we needed to assume linear effects for calculating the average willingness to pay and show differences between the classes. At the time of our study, there was a lack of literature describing the levels used for the attributes. Therefore, we considered the available literature and current discussion to derive the characteristics of the attributes. These data were discussed and approved by experts. Having a published qualitative study available would have led to a higher objectification of attribute and level selection. However, due to the short duration of the study, we had to forgo this possibility. In order to assess the relevance of the test conditions for nontest-savvy participants, an integration of an opt-out option was omitted. The study can be considered a feasibility study based on the number of participants. To extrapolate the results to the

whole country, the number of participants needs to be larger and nationally representative.

This study reports on the interest and preferences for WGS testing among Germans. Our study sample from the general population of Germany was aware of the importance of WGS results, and they preferred to make their data accessible for researchers but not for insurers because of possible discrimination. A positive attitude toward population-wide screening projects could therefore be assumed if data privacy is assured and the costs do not exceed €1,000. In general, the decision for or against a WGS is complex and could have far-reaching consequences. Hence, this decision should be a result of an informed consent process, where the attributes and consequences of a WGS are clarified.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Heard E, Tishkoff S, Todd JA, et al. Ten years of genetics and genomics: what have we achieved and where are we heading? *Nat Rev Genet*. 2010;11(10):723–733.
2. Bentley DR, Balasubramania S, Swerdlow HP, et al. Accurate whole human genome sequencing using reversible terminator chemistry. *Nature*. 2008;456(7218):53–59.
3. Vora T, Thacker N. Impacts of a biobank: bridging the gap in translational cancer medicine. *Indian J Med Paediatr Oncol*. 2015;36(1):17–23.
4. Rockman MV. Reverse engineering the genotype-phenotype map with natural genetic variation. *Nature*. 2008;456(7223):738–744.
5. Verma M. Personalized medicine and cancer. *J Pers Med*. 2012;2(1):1–14.
6. Meienberg J, Bruggmann R, Oexle K, Matyas G. Clinical sequencing: is WGS the better WES? *Hum Genet*. 2016;135(3):359–362.
7. Bodian DL, Klein E, Iyer RK, et al. Utility of whole-genome sequencing for detection of newborn screening disorders in a population cohort of 1,696 neonates. *Genet Med*. 2016;18(3):221–230.
8. Cho MK. Preventive genomic sequencing in the general population: do PGS fly? *Am J Bioeth*. 2016;15(7):1–2.
9. Ellingford JM, Barton S, Bhaskar S, et al. Whole genome sequencing increases molecular diagnostic yield compared with current diagnostic testing for inherited retinal disease. *Ophthalmology*. 2016;123(5):1143–1150.
10. EURAT Group. Cornerstones for an ethically and legally informed practice of Whole Genome Sequencing: Code of Conduct and Patient Consent Models: Project EURAT "Ethical and Legal Aspects of Whole Human Genome Sequencing". Available from: http://www.uni-heidelberg.de/md/totalsequenzierung/informationen/mk_eurat_position_paper.pdf. Accessed March 15, 2017.
11. Farrell PM, Kosorok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *Pediatrics*. 2001;107(1):1–13.
12. Strafford JC. Genetic testing for Lynch Syndrome, an inherited cancer of the bowel, endometrium, and ovary. *Rev Obstet Gynecol*. 2012;5(1):42–49.
13. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews(R)*. Seattle, WA: University of Washington, Seattle; 1993.
14. Vermeulen E, Henneman L, van El CG, Cornel MC. Public attitudes towards preventive genomics and personal interest in genetic testing to prevent disease: a survey study. *Eur J Public Health*. 2014;24(5):768–775.
15. Sanderson SC, Wardle J, Jarvis MJ, Humphries SE. Public interest in genetic testing for susceptibility to heart disease and cancer: a population-based survey in the UK. *Prev Med*. 2004;39(3):458–464.
16. Wilde A, Meiser B, Mitchell PB, Hadzi-Pavlovic D, Schofield PR. Community interest in predictive genetic testing for susceptibility to major depressive disorder in a large national sample. *Psychol Med*. 2011;41(8):1605–1613.
17. Berg S. The well-informed patient: a new breed of health care consumer. *Asthma Mag*. 2005;10(4):28–30.
18. Altman RB. Direct-to-consumer genetic testing: failure is not an option. *Clin Pharmacol Ther*. 2009;86(1):15–17.
19. Gollust SE, Wilfond BS, Hull SC. Direct-to-consumer sales of genetic services on the Internet. *Genet Med*. 2003;5(4):332–337.
20. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. *Pharmacoeconomics*. 2008;26(8):661–677.
21. Goldfeder RL, Priest JR, Zook JM, et al. Medical implications of technical accuracy in genome sequencing. *Genome Med*. 2016;8(1):24.
22. National Human Genome Research Institute. The Cost of Sequencing a Human Genome. Available from: https://www.genome.gov/sequencingcosts/. Accessed July 6, 2016; March 13, 2017.
23. Green ED, Guyer MS, National Human Genome Research Institute. Charting a course for genomic medicine from base pairs to bedside. *Nature*. 2011;470(7333):204–213.
24. Johnson KJ, Gehlert S. Return of results from genomic sequencing: a policy discussion of secondary findings for cancer predisposition. *J Cancer Policy*. 2014;2(3):75–80.
25. McLaughlin HM, Ceyhan-Birsoy O, Christensen KD, et al; MedSeq Project. A systematic approach to the reporting of medically relevant findings from whole genome sequencing. *BMC Med Genet*. 2014;15:134.
26. van Hoyweghen I, Horstman K. European practices of genetic information and insurance: lessons for the Genetic Information Nondiscrimination Act. *JAMA*. 2008;300(3):326–327.
27. Krinsky I, Robb AL. On approximating the statistical properties of elasticities. *Rev Econ Stat*. 1986;68(4):715–719.
28. German Federal Statistical Office. Bildungsstand der Bevölkerung. Available from: https://www.destatis.de/DE/Publikationen/Thematisch/BildungForschungKultur/Bildungsstand/BildungsstandBevoelkerung5210002167004.pdf?__blob=publicationFile. Accessed March 15, 2017.
29. German Federal Statistical Office [webpage on the Internet]. Einkommen und Einnahmen sowie Ausgaben privater Haushalte (Laufende Wirtschaftsrechnungen): Deutschland, Jahre, Haushaltsgröße. Available from: https://www-genesis.destatis.de/genesis/online;jsessionid=D950CB1AF32F174301847A1DC5FADC47.tomcat_GO_2_1?operation=previous&levelindex=2&levelid=1484292140539&step=2. Accessed March 15, 2017.
30. Institute of Medicine (US) Committee on Assessing Genetic Risks. *Assessing Genetic Risks: Implications for Health and Social Policy*. Washington, DC: National Academies Press (US); 1994.
31. Petersen BS, Fredrich B, Hoeppner MP, Ellinghaus D, Franke A. Opportunities and challenges of whole-genome and -exome sequencing. *BMC Genet*. 2017;18(1):14.
32. Hayden EC. Technology: the $1,000 genome. *Nature*. 2014;507(7492):294–295.
33. National Cancer Institute [webpage on the Internet]. BRCA1 and BRCA2: Cancer Risk and Genetic Testing. Available from: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Accessed March 16, 2017.

34. Lemke T. "A slap in the face". An exploratory study of genetic discrimination in Germany. *Genomics Soc Policy*. 2009;5:22–39.
35. Department of Health [webpage on the Internet]. The 100,000 Genomes Project. Available from: https://www.genomicsengland.co.uk/the-100000-genomes-project/. Accessed March 15, 2017.
36. Project Team SG. The Saudi Human Genome Program: an oasis in the desert of Arab medicine is providing clues to genetic disease. *IEEE Pulse*. 2015;6(6):22–26.
37. Boomsma DI, Wijmenga C, Slagboom EP, et al. The genome of the Netherlands: design, and project goals. *Eur J Hum Genet*. 2014;22(2):221–227.
38. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565–574.

Supplementary materials

Table S1 Overview of used variables

Topics	Variable	Meaning	Explanation	Characteristics	Type
DCE-specific variables	Questionnaire				
	Set				
	Seti		Questionnaire combined with set		
	Alternative			1	
				2	
	Choice			0: no	
				1: yes	
	Realn	Real decision (numeric)	Would you also choose the chosen alternative in reality?	0: no 1: yes	Numeric
Attributes	Att_TA	Test accuracy	Test accuracy	1: 90% 2: 95% 3: 99%	
	Att_DIS	Identified diseases	Test results	3: all 2: treatable diseases 1: serious hereditary disease	
	Att_TC	Test costs	Test costs	3: €1,500 2: €1,000 1: €500	
	Att_PROB	Probability of occurrence	Probability of occurrence of disease	1: 10% 2: 40% 3: 70%	
	Att_ACC	Access to data	Access to data	4: insurer and researcher 3: researcher 2: insurer 1: no one else	
Sociodemographic aspects	PersonID	Person identifier			
	Sex	Sex		1: male 2: female	Binary
	Age	Age			Numeric
	EDL	EDL	Highest level of education	0: no graduation 1: primary school 2: secondary school 3: high school 4: university	Numeric
	ES	ES		0: nonemployed 1: in training/student 2: employed/self-employed	Numeric
	INCn	INCn		0: no own income 1: <€1,000 2: €1,000–<€2,000 3: €2,000–<€3,000 4: €3,000–<€4,000 5: ³€4,000	Numeric
Health insurance and utilization of screening	SHI	Insurance		1: statutory 2: private	Binary
	PSC	PSC program		1: 1–2 times the year 2: every 2 years 3: every 5 years 4: every 10 years 5: never	Numeric
	PSChin	PSC program at full-cost coverage by health insurance		0: no 1: yes	Numeric
	PSCshare_r	PSC if health insurance pays a share	Recoded variable if Kostzu =1 or Kostal =1 then Kostzu_r =1	0: no 1: yes	Binary

(*Continued*)

Table S1 (*Continued*)

Topics	Variable	Meaning	Explanation	Characteristics	Type
	PSCsharen	PSC if health insurance pays a share (numeric)		0: no 1: yes	Numeric
	PSCpocketn	PSC on own payment (numeric)		0: no 1: yes	Numeric
Health status and diseases	HSn	Subjective HSn		1: very bad 2: bad 3: medium 4: good 5: very good	Numeric
	FHD	Known FHD		0: no 1: yes	Binary
	FHDfree	Open questions to hereditary diseases in the family		Free text	Free text
	CHIn	CHIn		0: no 1: yes	Binary
	DCHIn	DCHIn		0: no 1: I do not know 2: yes	Numeric
	AFHD	AFHD		0: no 1: yes	Numeric
	AFHDfree	Fear of which hereditary disease		Free text	Free text

Abbreviations: AFHD, afraid of hereditary disease; CHIn, children (numeric); DCHIn, desire to have children (numeric); FHD, family hereditary disease; EDL, educational level; ES, employment status; HSn, health status (numeric); INCn, income (numeric); PSC, participation in screening; SHI, social or private health insurance.

Table S2 Overview of included independent variables used in GLMM and LCMLM

Model	Dependent variable	Independent variables tested	Mixed effects	Lean model
GLMM (for both participants and full-sample)	Choice	Att_TA + Att_DIS + Att_TC + Att_PROB + Att_ACC, ES × EDL, KF, AFHD, CHI, DCHI, SE, HSn, PSC	PersonID, serial, Set, Seti, age, sex, EDL, ES	Wahl ~ Att_TA + Att_DIS + Att_TC + Att_PROB + Att_ACC + ES × EDL + (1|Seti)
LCMLM	Choice	Att_TA + Att_DIS + Att_TC + Att_PROB + Att_ACC	PersonID, Att_TA + Att_DIS + Att_TC + Att_PROB + Att_ACC, classmb: age, sex, SHI, ES, EDL, INCn, HSn, PSC, KF, AFHD, CHI, DCHI, Kostzu_r, EDL × HSn	Wahl ~ Att_TA + Att_DIS + Att_TC + Att_PROB + Att_ACC, random = ~ Seti, subject = "PersonID", mixture = ~ Att_TA + Att_DIS + Att_TC + Att_PROB + Att_ACC, classmb = ~ sex + EDL + INCn + HSn, ng =2, data = Daten, link = "linear"
GLMM real	Real	Datentn$Att_TA + Datentn$Att_DIS + Datentn$Att_TC + Datentn$Att_PROB + Datentn$Att_ACC	PersonID Datentn$sex + Datentn$age, +PSCpocketn + SHI, EDL+ES + INCn + PSC + Kostzu_r + Khf + CHIn + HSn + DCHIn + PSC, AFHD	Real ~ Att_TC + Att_PROB + Att_ACC + EDL + ES + INCn + Kostzu_r + AFHD (1|PersonID)

Abbreviations: AFHD, afraid of hereditary disease; CHI, children; CHIn, CHI (numeric); DCHIn, desire to have children; DCHIn, DCHI (numeric); EDL, educational level; ES, employment status; GLMM, generalized linear mixed-effects model; HSn, health status (numeric); INCn, income (numeric); KL, known familar hereditary diseases; LCMLM, latent class mixed logit model; PSC, participation in screening; SHI, social or private health insurance.

Table S3 Latent class mixed logit model results – attribute effects

Attributes and levels	Class 1 (higher proportion of men)			Class 2 (higher proportion of woman)		
	β coefficient	SE	*P*-value	*β* coefficient	SE	*P*-value
Test accuracy						
90%	–0.002	0.04244	0.962	–0.234	0.03229	0.000
95%	0.079	0.03596	0.027	0.015	0.03102	0.634
99% (ref)	–0.081			–0.248		
Identified diseases						
All diseases	0.082	0.0405	0.043	0.137	0.03581	0.000
Treatable diseases	–0.078	0.03621	0.030	–0.088	0.03373	0.009
Serious hereditary disease (ref)	0.160			0.225		
Test costs						
€1,500	–0.216	0.03467	0.000	–0.151	0.03073	0.000
€1,000	–0.016	0.03283	0.620	0.108	0.03043	0.000
€500 (ref)	–0.200			–0.259		
Probability of occurrence						
10%	0.158	0.03623	0.000	–0.398	0.0341	0.000
40%	0.075	0.03431	0.029	0.007	0.03158	0.834
70% (ref)	0.083			–0.404		
Access to data						
Insurer and researcher	–0.200	0.04125	0.000	0.142	0.03933	0.000
Researcher	0.282	0.03912	0.000	0.314	0.03644	0.000
Insurer	–0.478	0.04563	0.000	–0.043	0.03765	0.258
No one else (ref)	0.760			0.357		
Intercept						
	0	NA	NA	–0.01679	0.0276	0.54311

Notes: Adjusted for class-membership effects, sex, educational level, and income; subject, "PersonID".
Abbreviations: SE, standard error; NA, not applicable.

Table S4 Results from the generalized linear mixed-effects model

Topics	Variables	Levels	Full sample			Potential users		
			β coefficient	SE	*P*-value	*β* coefficient	SE	*P*-value
Attributes	Test accuracy	90%	–0.330	0.050	0.000	–0.251	0.072	0.000
		95%	0.120	0.051	0.020	0.028	0.075	0.709
		99% (ref)	–0.450			–0.279		
	Identified diseases	All diseases	0.228	0.049	0.000	0.496	0.071	0.000
		Treatable diseases	–0.259	0.050	0.000	–0.386	0.073	0.000
		Serious hereditary disease (ref)	0.487			0.882		
	Test costs	€1,500	–0.515	0.051	0.000	–0.497	0.073	0.000
		€1,000	0.067	0.046	0.148	–0.013	0.067	0.842
		€500 (ref)	–0.582			–0.483		
	Probability of occurrence	10%	–0.411	0.051	0.000	–0.373	0.073	0.000
		40%	0.100	0.050	0.043	0.092	0.072	0.199
		70% (ref)	–0.511			–0.466		
	Access to data	Insurer and researcher	–0.011	0.062	0.860	–0.033	0.089	0.709
		Researcher	0.755	0.065	0.000	0.554	0.092	0.000
		Insurer	–0.812	0.067	0.000	–0.636	0.102	0.000
		No one else (ref)	0.046			0.049		
Person-specific data	Employment		0.000	0.131	1.000	–0.007	0.342	0.983
	Educational level		0.000	0.076	1.000	–0.006	0.194	0.975
	Employment × educational level		0.000	0.045	1.000		0.106	0.981
	Intercept		0.007	0.258	0.978	0.020	0.654	0.975

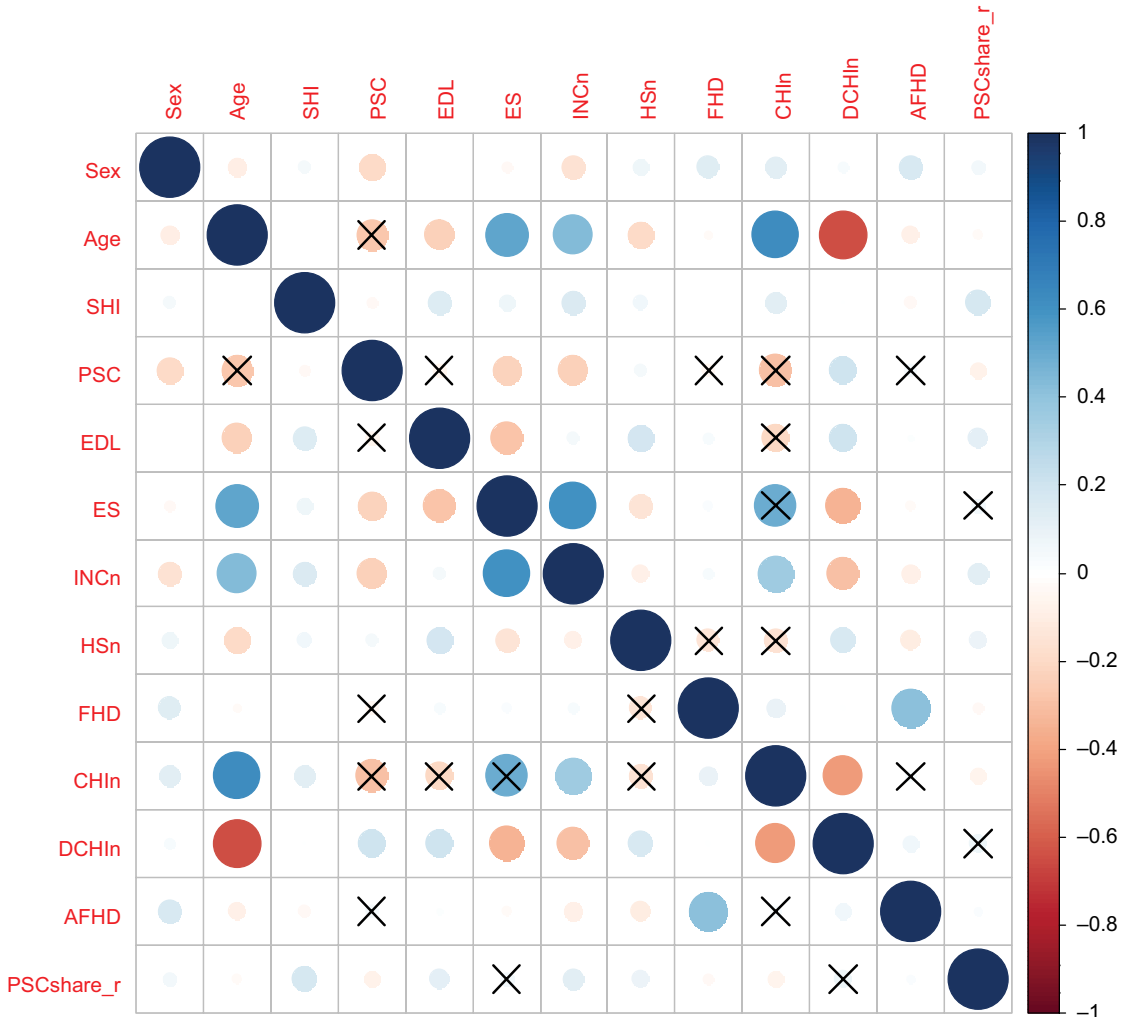

Figure S1 Correlation plot of independent variables.
Notes: The significance level was a *P*-value of 0.05. X: not significant correlations. Dark blue indicates highly positive correlations. Dark red indicates highly negative correlations. Larger circles indicate higher correlations. PSCshare_r, PSC if health insurance pays a share.
Abbreviations: AFHD, afraid of hereditary disease; CHIn, children (numeric); DCHIn, desire to have children (numeric); EDL, educational level; ES, employment status; FHD, family hereditary disease; HSn, health status (numeric); INCn, income (numeric); PSC, participation in screening; SHI, social or private health insurance.

Modul 8

Humangenetische Beratungen im Rahmen prädiktiver genetischer Diagnostik – Eine Analyse der verfügbaren Kapazitäten im deutschen Setting

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Humangenetische Beratungen im Rahmen prädiktiver genetischer Diagnostik – Eine Analyse der verfügbaren Kapazitäten im deutschen Setting

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Zusammenfassung

Hintergrund: Sowohl die Einsatzmöglichkeiten von genetischer Diagnostik als auch das Interesse der Bevölkerung an prädiktiven genetischen Analysen wird immer größer. Genetische Beratungen stellen einen obligaten Bestandteil im qualitätsgesicherten Versorgungsprozess dar, um eine informierte Einwilligung in Bezug auf die Durchführung, Chancen und Risiken als auch die Ergebnisinterpretation gewährleisten zu können.

Ziel der Arbeit: Die Analyse der aktuell verfügbaren Beratungskapazitäten wurde im Kontext prädiktiver Analysen, für die zwei genetische Beratungen gesetzlich verpflichtend sind, evaluiert.

Methoden: Basierend auf Daten der Bundesärztekammer von 2015 wurde eine Kapazitätsanalyse der aktuell verfügbaren Beratungskapazitäten durchgeführt. Kapazitätsveränderungen durch unterschiedliche Anteile des Beratungsaufwandes an der Arbeitszeit im ambulanten und stationären Setting als auch Differenzierungen des Beratungsaufwandes pro Fall, wurden mit Hilfe von Sensitivitätsanalysen simuliert.

Ergebnisse und Diskussion: Die Kapazitätsanalyse ergab mit einem mittleren Beratungsumfang von 105 Minuten je Analyse eine jährlich mögliche Fallzahl von 143.520 prädiktivgenetischen Analysen. In 2015 könnten ca. 19 % der Neugeborenen und 0,17% der deutschen Bevölkerung unter der Restriktion der begrenzten Beratungskapazitäten einer prädiktivgenetischen Analyse unterzogen werden. Faktoren, wie die Ausweitung der Einsatzmöglichkeiten und die Kostensenkungen von genetischen Analysen werden perspektivisch die Attraktivität von prädiktiven Genanalysen steigern. Dieser steigenden Nachfrage steht jedoch eine kleine Anzahl von Humangenetikern gegenüber. Strukturelle Anpassungen sind somit zukünftig notwendig um einem potentiell drohenden Engpass entgegen zu wirken.

Schlüsselwörter: Genetische Beratung; Kapazitätsanalyse; Prädiktion; Humangenetiker; Genetischer Berater; Genetische Diagnostik

Abstract

Background: The application possibilities of genetic diagnostic as well as the interest of the population in predictive genetic analyzes are steadily increasing. Genetic counselling is in a quality-assured care process obligatory. Thus, an informed consent regarding to opportunities, risks and interpretation of results can be ensured.

Aim: An evaluation of the currently available counseling capacities in the context of predictive genetic analyzes, for which two genetic counseling sessions are legally compulsory.

Methods: Based on data from the German Medical Association in 2015, a capacity analysis of the currently available consulting capacities was conducted. Capacity changes due to different proportions for counselling on working time in in- and outpatient care as well as differences in counselling time per case were simulated by sensitivity analysis.

Findings and Discussion: The capacity analysis resulted in a possible yearly case number of 143,520 for predictive genetic analysis by an average consultation time of 105 minutes per analysis. In 2015 approximately 19 % of all newborns and only 0.17 % of the general German population could be undergo a predictive genetic analysis under the restriction of limited counseling capacities. Aspects, such as the extension of application possibilities and cost reductions of genetic analysis will lead to an increasing attractiveness of predictive genetic analysis in future. This growing demand for genetic analysis is being countered by a small number of human geneticists. Structural adaptations will be necessary to counteract the potential bottleneck.

Keywords: Genetic counselling; capacity analyses; prediction; human genetic expert; genetic counsellor; genetic diagnostics

Hintergrund

Genetische Diagnostik kann als das zentrale Werkzeug der zukünftigen medizinischen Versorgung angesehen werden. Der medizinisch technische Fortschritt und die stetigen Wissens- und Erkenntniszugewinne führen nicht nur zu einer Ausweitung der Applikationsgebiete sondern auch zu stetig wachsenden Möglichkeiten in den Bereichen von Therapie und Prävention [1]. Die derzeitigen Möglichkeiten sind bereits mannigfaltig und reichen von der diagnostischen Abklärung auf molekulargenetischer Basis (z.B. seltene Erkrankungen oder Spezifikation bzw. Klassifikation einer onkologischen Erkrankung) [2, 3] über Wirksamkeitstests im Vorfeld einer Medikamentenapplikation (z.B. mit dem Ziel der Reduktion von unerwünschten Nebenwirkungen oder zur Bestimmung der Ansprechrate auf spezifische Chemotherapeutika etc.)[4] bis hin zu prädiktiven Analysen (z.B. Abklärung von hereditären Mutationen beim Neugeborenen und in pränatalen Untersuchungen oder prädiktiven Analysen zur Identifikation von Erkrankungsdispositionen) [5–7]. Vermehrte Bestrebungen konnten bereits auch im Bereich der Gentherapie verzeichnet werden. 2014 erfolgte bspw. erstmals die Zulassung eines gentherapeutischen Medikaments im Bereich der Ophthalmologie zur Behandlung eines angeborenen Lipoproteinlipase-Defizits [8].

Die Integration bzw. Anwendung dieser genotyp-basierten Applikationsmöglichkeiten erfordert in der klinischen Versorgung sowohl die Berücksichtigung von rechtlichen, ethischen und ökonomischen Aspekten als auch die Bereitstellung diverser organisatorischer Strukturen und Kapazitäten [9]. Im Jahr 2010 wurde das deutsche Gendiagnostikgesetz (GenDG) erlassen und regelt seither u.a. die genetischen Untersuchungen zu medizinischen Zwecken. Regelungsgegenstände sind hierbei bspw. neben dem Arztvorbehalt (§ 7 GenDG), der Aufklärung (§ 9 GenDG), der Verwendung und Vernichtung genetischer Proben (§ 13 GenDG) auch die Erfordernisse, welche an eine genetische Beratung (§ 10 GenDG) gestellt werden. Die genetische Beratung soll für den „Patienten“ bzw. Durchführenden die Möglichkeit schaffen über Risiken, das Durchführungsprozedere und die potentiellen Ergebnisse und daraus resultierenden Folgen sowohl für die eigene Person als auch für die Familienmitglieder aufgeklärt zu werden [10, 11]. Eine unzureichende Aufklärung und Beratung kann zu erheblichen Folgen für die Ratsuchenden führen. Es besteht die Gefahr, dass die Sequenzierten zu sogenannten „gesunden Kranken“ werden und durch Verängstigung oder Furcht negative Lebensqualitätseffekte bedingt werden [12, 13]. Zudem stellt die humangenetische Beratung ein essentielles Instrument dar, um den Interessierten eine informierte Einwilligung in Bezug auf die Durchführung, Chancen, Risiken und Auswirkungen zu ermöglichen [14, 9].

Die humangenetische Beratung vor und nach der Durchführung einer genetischen Analyse wurde somit zum obligaten Bestandteil einer qualitätsgesicherten Versorgungspraxis. Nicht nur durch die steigende Anzahl der genetischen Analysen in einer Vielzahl von Indikationsgebieten [15], sondern auch durch die Zunahme der Komplexität der Beratungen [16–18] aufgrund der nicht-intendierten Befunde könnte es zukünftig zu strukturellen Engpässen in der Versorgung kommen.

Mit Hilfe dieser Analyse soll veranschaulicht werden, für welche Anzahl an genetischen Beratungen im Rahmen von prädiktiven indikationsunabhängigen Analysen die aktuell im deutschen Setting vorherrschenden humangenetischen Strukturen ausgelegt sind.

Humangenetische Beratung nach § 10 GenDG

§ 10 GenDG stellt die Regelungsgrundlage der humangenetischen Beratung dar. Dabei werden vom Gesetzgeber die notwendigen fachlichen Anforderungen nach Analyseart bzw. Untersuchungsintention unterschieden. Während genetische Analysen zur diagnostischen Abklärung von Ärzten ohne humangenetische Fachausbildung initiiert werden dürfen und die genetische Beratung als fakultatives Angebot zu verstehen ist, bedürfen prädiktive genetische Analysen einer Veranlassung von Ärzten mit entsprechender humangenetischer Qualifikation. Eine humangenetische Beratung ist somit vor- und nach einer genetischen Analyse auf Grundlage des § 10 Abs. 2 GenDG notwendig. Nach dieser gesetzlichen Grundlage ergeben sich somit folgende Anwendungs- bzw. Regelungsbereiche, bei welchen eine humangenetische Beratung mittels eines Facharztes für Humangenetik notwendig werden: (1) Abklärung von erblich-bedingten Erkrankungen (monogene Erkrankungen)- (1a) indikationsspezifische und (1b) indikationsunabhängige Analysen (z.B. genetisches Neugeborenenscreening), (2) Prädiktive indikationsspezifische Analysen (z.B. onkologische und kardiovaskuläre Dispositionen) und (3) vorgeburtliche Untersuchungen. Im Anschluss an eine genetische Analyse ist eine abschließende Ergebnisbeurteilung mit genetischer Beratung, vor allem im prädiktiven Kontext, ein obligater Bestandteil des genetischen Diagnostikprozesses.

Aktuelle verfügbare Beratungskapazitäten

Basierend auf Daten der Bundesärztekammer gab es im Jahr 2015 208 berufstätige Humangenetiker, wobei 135 im ambulanten und 88 von diesen im stationären Setting tätig waren. Weitere 18 waren bspw. in Behörden, Körperschaften oder sonstigen Bereichen tätig [19]. Für die Berechnung der aktuell verfügbaren humangenetischen Beratungskapazitäten werden diese 18 Humangenetiker aufgrund einer angenommenen fehlenden direkten Versorgungsrelevanz aus der Kalkulation exkludiert. Der prozentuale Anteil humangenetischer Beratungen an der Arbeitszeit eines Humangenetikers divergiert zwischen dem stationären und ambulanten Setting.

Es wird die Annahme getroffen, dass im stationären Setting, aufgrund bspw. labortechnischer Arbeiten, Forschung und Lehre, weniger zeitliche Ressourcen für humangenetische Beratungen im Vergleich zur ambulanten Versorgung zur Verfügung stehen. Für die Basis-Kalkulation wird deshalb im stationären Setting von einem Beratungsanteil von 40% an der Gesamtarbeitszeit ausgegangen und im ambulanten Setting von 80%. Diese Beratungskapazitäten werden mittels Sensitivitätsanalysen in 10 %-Schritten variiert, sodass im ambulanten Setting auch Aussagen zu geringeren und im stationären Setting zu höheren Beratungskapazitäten getroffen werden können. Zudem wird eine Arbeitszeit von 42 h/Woche entsprechend des Tarifvertrages für Ärzte des Bundeslandes Niedersachsen [20] und eine Anzahl von 46 Arbeitswochen/Jahr angenommen. Für eine Beratung vor als auch nach der genetischen Untersuchung sind Expertenschätzungen zufolge jeweils 45-60 Minuten notwendig [21]. Im Mittel ergibt sich somit ein Beratungsaufwand von 105 Minuten bzw. 1,75 Stunden für die beiden obligatorischen humangenetischen Beratungen im Rahmen einer prädiktiven Analyse. Für eine retrospektive Bedarfsanalyse von notwendigen Kapazitäten für humangenetische Beratungen werden als Referenz für Vergleiche zum einen (1) die Geburtenzahlen des Jahres 2015 und zum anderen (2) die Bevölkerungsanzahl des Jahres 2015 auf Basis des Statistischen Bundesamtes herangezogen [22]. Somit kann eine Aussage dazu getroffen werden, wie viele der 737.575 Neugeborenen im Hinblick auf die aktuell verfügbaren Beratungskapazitäten einer breiten indikationsunabhängigen genetischen Analyse unterzogen werden können oder für welchen prozentualen Anteil der deutschen Bevölkerung (82,18 Millionen Menschen) humangenetische prädiktive Analysen im Hinblick auf die zwei obligaten Beratungen verfügbar gewesen wären.

Aktuell verfügbare Kapazitäten für humangenetische Beratungen

Die *Tabelle 1* stellt die Kapazitätsanalyse in der Basis-Kalkulation dar. Bei einer Arbeitszeitaufwendung von 80% im ambulanten und 40% im stationären Setting für humangenetische Beratungen ergeben sich insgesamt 251.160 Beratungsstunden pro Jahr. Bei einem mittleren Beratungsaufwand von 105 Minuten bzw. 1,75 Stunden pro Fall ergibt sich eine jährliche Kapazität von 143.520 für genetische prädiktive Analysen.

[Tabelle 1]

Wird diese Kapazitätsbeschränkung bei der gegebenen Basis-Kalkulation in das Verhältnis zur Anzahl der Neugeborenen gesetzt, bedeutet dies, dass ca. 19% der Neugeborenen einer umfassenden prädiktiven genetischen Analyse unterzogen werden können bzw. deren Eltern der verpflichtende Beratungsumfang zur Verfügung steht. Bezogen auf die deutsche Gesamtbevölkerung können jährlich unter gegebenen Bedingungen lediglich ca. 0,17 % der Bevölkerung eine prädiktive genomweite Analyse unter der Restriktion bzw. Voraussetzung einer mittleren Bera-

tungsdauer sowohl für die prä- als auch für die postanalytische humangenetische Beratung durchführen lassen. Eine Fallzahlanpassung unter Variation der Beratungsdauer wird in der in *Figur 1* dargestellten Sensitivitätsanalyse simuliert. Eine Reduktion auf die untere Beratungsdauer (90 Minuten bzw. 1,5 Stunden) führt zu einer Kapazitätserweiterung um ca. 16,6% auf 167.440 genetische Analysen pro Jahr. Im Gegensatz hierzu führen umfangreichere Beratungen (120 Minuten bzw. 2 Stunden) zu einer Reduktion der beratungsbedingten Durchführungskapazitäten um etwa 12,5% auf 125.580 jährliche Fälle.

[Abbildung 1]

Diskussion

Die vorliegende Analyse zur Bedarfsermittlung der Kapazitäten für humangenetische Beratungen verdeutlicht allein am Beispiel des Neugeborenenscreenings ein potentiell drohendes strukturelles Defizit in der humangenetischen Versorgung.

In diesem Bereich trifft eine der zahlenmäßig kleinsten Facharztgruppen auf einen Versorgungsbereich, welcher zukünftig die Ausgangsbasis für eine Vielzahl von präventiven und therapeutischen Entscheidungen darstellen könnte und somit mit einem stetig wachsenden Bedarf an genetischen Beratungen einhergeht [23, 24].

Um dem Mangel an Fachärzten für Humangenetik und Ärzten mit der Zusatzbezeichnung Medizinische Genetik entgegenzuwirken, veranlasste im Jahr 2011 die Gendiagnostik-Kommission (GEKO), die „Qualifikation zur fachgebundenen genetischen Beratung“. Die GEKO ist eine interdisziplinäre und unabhängige, beim Robert-Koch-Institut angesiedelte Kommission und nach § 23 des GenDG für die Erarbeitung der Ausführungsbestimmungen des GenDG zuständig. Seither bedürfen genetische Beratungen einer ärztlichen Person, welche sowohl die Voraussetzungen des § 7 Abs. 1 und 3 GenDG als auch der GEKO-Richtlinie erfüllt. Die fachgebundene genetische Beratung richtet sich an Fachärzte des jeweiligen Indikationsgebietes. Eine Ausbildung beträgt 72 Stunden und umfasst dabei einen Basisteil (genetische Grundlagen, methodische Aspekte, Risikoermittlung), psychosoziale und ethische Aspekte als auch des fachspezifische Inhalte [25].

Durch diese Maßnahme können die Kapazitäten an ärztliche-genetischer Beratung zwar indikationsspezifisch erweitert werden, jedoch bleibt die Frage nach der Sicherstellung der genetischen Beratung im Falle von indikationsunabhängigen Anwendungsgebieten und somit ohne eine spezifische Fragestellung, wie bspw. im Falle eines genomweiten genetischen Neugeborenenscreenings.

Unabhängig von der Erweiterung des Kreises der zur Durchführung einer genetischen Beratung Befugten, muss die durch das prädiktive Potential gestiegene Komplexität der Beratung [26]

Berücksichtigung finden. Spezifische genetische Analysen gehen mit einem deutlichen geringeren Beratungsaufwand einher, da sich diese entweder auf Einzelgenanalysen beschränken [27] oder Filter bei umfangreicheren Analysen weitere von der Fragestellung unabhängige Befunde, sogenannte Zufallsbefunde [28], ausselektieren [29]. Hingegen werden bei indikationsunabhängigen Analysen oder Analysen, welche sich auf eine bis dato unbekannte Ursache richten, umfangreichere Analysen, wie bspw. die Sequenzierung des Exoms oder des Genoms durchgeführt. Diese weisen eine größere „Sequenzierungstiefe" auf und besitzen somit ein deutlich größeres Potential prädiktive Befunde zu generieren. Die Interpretation dieser Befunde bedarf einer umfangreichen Berücksichtigung diverser Faktoren. Nach dem derzeitigen Wissenstand existieren nur wenige Mutationen bzw. genetische Variationen, wie bspw. Chorea Hungtington [30], bei welchen mit einer Wahrscheinlichkeit von 100% eine Erkrankungsmanifestation vorausgesagt werden kann. Interaktionen zwischen den einzelnen Mutationen bzw. Genen (Kompensation oder Verstärkung der Funktion) [31–33], wenig bekannte Einflussfaktoren für die phänotypische Krankheitsausbildung [34], die Berücksichtigung der Sensitivitäts- und Spezifitätswerte [35] etc. sind nur einige Aspekte, welche die Interpretation der Analyseergebnisse erschweren.

Im Jahr 2013 haben laut der GfH 15 Teilnehmer die Qualifikationsmaßnahme zur fachgebundenen genetischen Beratung erfolgreich abgeschlossen [36]. Die Ausweitung des zur genetischen Beratung befugten Personenkreises stellt einen wichtigen Schritt zur Sicherstellung einer qualitätsgesicherten humangenetischen Versorgung dar. Inwieweit diese Ausweitung der durch den Trend der personalisierten und individualisierten Medizin gestiegenen Nachfrage nach genetischen Beratungen gerecht werden kann, ist unter diversen Gesichtspunkten zu betrachten. Das Kalkulationsbeispiel betrachtete die genomweite Analyse von Neugeborenen und bereits bei einem Sequenzierungsanteil von lediglich 10% aller Neugeborenen in 2015, erreichen die aktuellen Kapazitäten ihre Grenzen. Diverse Studien belegen das Interesse der Bevölkerung an genetischen Analysen [37, 38]. Die Detektion bzw. der Ausschluss von genetischen familiären Dispositionen steht hierbei im primären Fokus. Zum aktuellen Zeitpunkt übernehmen bspw. bereits eine Vielzahl an Krankenkassen nicht nur die Genanalysen zur Detektion von BRCA I und BRCA II bei familiären Mamma- und Ovarialkarzinomen sondern auch weiterführende Maßnahmen, wie Mastektomie und Mamma-Rekonstruktionen [39]. Hierbei handelt es sich um familienanamnetisch-induzierte Einzelgenanalysen, welche hinsichtlich der Beratung dem Regelungsbereich der fachgebundenen humangenetischen Analyse/Beratung unterliegen. Einigen Studien zufolge wächst allerdings auch das Interesse an genomweiten Analysen, wie Exom- und Genomsequenzierungen [39, 40]. Da bei diesen kein konkreter Indikationsbezug vorherrscht unterliegen diese Analysen im prädiktiven Kontext genetischen Beratungen von Fachärzten für Humangenetik.

Die erhebliche Relevanz qualifizierter genetischer Beratungen bleibt unumstritten. Eine umfassende genetische Beratung hinsichtlich der Chancen und Risiken im Vorfeld als auch der qualifizierten Ergebnisinterpretation im Nachgang einer genetischen Analyse ist für den Interessierten/Sequenzierten und dessen Angehörigen essentiell. Den Interessierten wird somit eine informierte Einwilligung ermöglicht und versetzt diesen sogleich in die Lage die Konsequenzen einer genetischen Analysen abschätzen und die Aussagekraft probabilitischer Befunde in den Erkrankungskontext einordnen zu können [9].

Länder, in welchen genetische Analysen zum aktuellen Zeitpunkt einen größeren Verbreitungsgrad in der medizinischen Versorgung besitzen, können als Organisations- und Strukturvergleich herangezogen werden. Im Falle von potentiell notwendigen Kapazitätsausweitungen, aufgrund des steigenden Beratungsbedarfs, können Strukturveränderungen nach internationalen Vorbildern durchgeführt bzw. angepasst werden. Im Hinblick auf genetische Beratungen haben viele Länder innerhalb (z.B. Belgien, Dänemark, Finnland, Frankreich, Großbritannien, Island, Italien, Niederlande, Norwegen, Portugal, Rumänien, Slowenien, Spanien, Schweden, Schweiz, Türkei, Zypern) als auch außerhalb Europas (Australien, Kanada, Neuseeland, Südafrika, USA, Chile, Kuba, Saudi-Arabien, Israel, Japan, Taiwan) genetische Berater als anerkannten Ausbildungsberuf implementiert. In Deutschland und einigen anderen wenigen Ländern (z.B. China, Indien, Ungarn, Brasilien) ist dies allerdings kein anerkannter Ausbildungsberuf [41] und die genetische Beratung unterliegt dem Arztvorbehalt (§ 7 Nr. 3 GenDG). Der Erkenntnisfortschritt in der genetischen Versorgung bedarf jedoch komplexer werdender Beratungen, welche einer zu kleinen Anzahl von qualifizierten Ärzten gegenüber standen bzw. noch immer stehen [41]. Die durchgeführte Kapazitätsanalyse verdeutlicht im Falle von stetig wachsenden Nachfragen nach prädiktiven genetischen Analysen ein drohendes strukturelles Defizit im Hinblick auf die genetischen Beratungsstrukturen. Eine potentielle Lösung bzw. Entlastung dieser Facharztgruppe könnte durch die Integration nicht-ärztlicher Mitarbeiter in den Beratungsprozess erzielt werden. Die Ausbildung von genetischen Beratern divergiert hierbei zwischen einzelnen Ländern. Während in Deutschland ein Studium zum Facharzt für Humangenetik Voraussetzung für genetische Beratungen ist, existieren bspw. in Frankreich [42] spezielle Masterstudiengänge für genetische Berater und in Dänemark können Krankenschwestern, Laboranten, Hebammen etc. die genetische Beratung durchführen. Der Eintrag in zertifizierte „Genetic Counesllor Registration Bords (GCRB)“ wie z.B. in Großbritannien kann dabei als ein Instrument der Sicherstellung der Qualifizierung bzw. Qualitätssicherung dienen [43]. Abhängig vom jeweiligen System arbeiten Genetische Berater außerhalb des Aufsichtsbereiches des Arztes (z.B. in Frankreich, den Niederlanden, Norwegen, Türkei) oder in Zusammenarbeit mit dem behandelnden Arzt (z.B. Island, Dänemark, Irland, Schweden, Großbritannien) [42]. Multidisziplinäre Teams haben sich dabei als ein wichtiger Faktor einer effizienten Durchführung von genetischen Analysen erwiesen [44].

Die Aufgaben genetischer Beratung stellen die Vermittlung notwendiger Informationen, die Unterstützung zu einer eigenständigen Entscheidung die genetische Analyse durchführen zu lassen und die emotionale Unterstützung bei der Verarbeitung der Diagnose dar [43]. Genetische Diagnosen obliegen weiterhin dem Facharzt [42].

Der Bedarfsplanungsrichtlinie zu Folge ist im Bereich der Humangenetik zu aktuellen Zeitpunkt keine Unterversorgung erkennbar [45]. Bedingt durch die zunehmende Nachfrage nach genetischen Analysen und der zunehmenden Komplexität von Beratungen aufgrund des Erkenntnisfortschritts werden perspektivisch möglicherweise Anpassungen notwendig. Eine Erweiterung des zur genetischen Beratung befugten Personenkreises unter Wahrung des Arztvorbehalts oder die Implementierung von genetischen Beratern stellen dabei zwei mögliche Optionen dar, genetischen Beratungen im Trend einer genotyp-basierten Medizin gerecht zu werden. Um die Anzahl der ärztlichen Berater zu erhöhen, könnten Ausbildungsmöglichkeiten, welche diese auch für indikationsunabhängige Beratungen legitimeren oder Anreize für das Studium zum Humangenetiker (z.B. Vergütungen von Famulaturen, Stipendienprogramm des Strukturfonds zur Sicherstellung der ärztlichen Versorgung, Vergütungsanreize) [46] geschaffen werden. Auf der anderen Seite könnte ein Ausbildungsberuf zum genetischen Berater aufgrund der kürzeren Ausbildungsdauer (zwei jähriges Masterprogramm zum Genetic Counselling M.Sc. [47]) nicht nur auf eine steigende Nachfrage flexibler reagieren sondern stellt auch eine kostengünstigere Alternative im Vergleich zur fachärztlichen Beratung dar. Bereits kurzfristig könnte dies zu einer Entlastung der Solidargemeinschaft aufgrund der kostengünstigeren Durchführung führen. Eine Anzahl von 4.000 zugelassenen genetischen Beratern in den USA verdeutlicht die Relevanz dieses Berufs im Kontext der genotyp-basierten Medizin [48] vor allem im Hinblick auf den in vielen Ländern identifizierten bzw. prognostizierten Engpass an genetischen Beratern [49, 50].

Der vorliegenden Kapazitätsanalyse liegen Limitationen zugrunde. Die Analyse wurde lediglich für Beratungen im prädiktiven Kontext, welche zwei humangenetischen Beratungen erfordern, durchgeführt. Um ein realistisches Abbild der Kapazitätsbegrenzungen zu erhalten, ist ebenfalls eine additive Betrachtung der durch Humangenetiker durchgeführten Beratungen im genetisch-diagnostischen Kontext notwendig. Diese konnten aufgrund der aktuell fehlenden Datenlage im Hinblick auf die durch Humangenetiker durchgeführten genetischen Beratungen im prädiktiven, prognostischen und diagnostischen Kontext als auch der generell durchgeführten Anzahl an genetischen Beratungen (inklusive der fachgebundenen genetischen Beratung) nicht adäquat abgebildet werden. Durch eine additive Betrachtung ist jedoch von einer Reduktion der berechneten Kapazitäten auszugehen. Weiterhin handelt es sich bei dieser Analyse um eine Kalkulation im Maximalansatz. Die ebenfalls fehlende Studienlage zur Anzahl der durchgeführten genetischen Analysen bzw. der Anzahl potentiell an genetischen Analysen Interessierter erschwerte

eine Analyse anhand des aktuellen Bedarfs. Zudem bleiben Weiterbildungsassistenten, welche sich in der Facharztausbildung zum Humangenetiker befinden und auch schon während dieser Ausbildungszeit humangenetische Beratungen durchführen, aufgrund der fehlenden Datenlage von der Analyse unberücksichtigt. Eine Berücksichtigung hätte einen positiven Einfluss auf die Kapazitätskalkulation.

Fazit

Der Trend einer Medizin deren Grundstein auf dem genetischen Profil des Patienten fußt, wird sich weiter fortsetzen. Eine qualifizierte und gesicherte Beratung bildet dabei den essentiellen Grundstein für informierte Entscheidungen für bzw. gegen eine genetische Analyse, deren Umfang sowie der Ergebnisinterpretation und Unterstützung im Umgang mit der Diagnose. Der stetig steigenden Nachfrage an genetischen Analysen steht eine kleine Anzahl von zur genetischen Beratung befugten Ärzten gegenüber. Es ist mittelfristig eine Aufgabe des Gesetzgebers mit strukturellen Anpassungen einem potentiell drohenden Defizit an genetischen Beratungen entgegen zu wirken.

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Literatur

1. Katsanis SH, Katsanis N (2013) Molecular genetic testing and the future of clinical genomics. Nature reviews. Genetics 14(6): 415–426. doi: 10.1038/nrg3493
2. Schwartz MD, Lerman C, Brogan B et al. (2004) Impact of BRCA1/BRCA2 counseling and testing on newly diagnosed breast cancer patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 22(10): 1823–1829. doi: 10.1200/JCO.2004.04.086
3. Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE (2013) Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nature reviews. Genetics 14(10): 681–691. doi: 10.1038/nrg3555
4. Moaddeb J, Haga SB (2013) Pharmacogenetic testing: Current Evidence of Clinical Utility. Therapeutic advances in drug safety 4(4): 155–169. doi: 10.1177/2042098613485595
5. Khoury MJ, McCabe LL, McCabe ERB (2003) Population screening in the age of genomic medicine. The New England journal of medicine 348(1): 50–58. doi: 10.1056/NEJMra013182
6. Krones T, Schlüter E, El Ansari S, Wissner T, Zoll R, Richter G (2004) Präimplantationsdiagnostik, Pränataldiagnostik und Schwangerschaftsabbruch. Gynäkologische Endokrinologie 2(4): 245–250. doi: 10.1007/s10304-004-0075-4
7. Walther A, Johnstone E, Swanton C, Midgley R, Tomlinson I, Kerr D (2009) Genetic prognostic and predictive markers in colorectal cancer. Nature reviews. Cancer 9(7): 489–499. doi: 10.1038/nrc2645
8. Salmon F, Grosios K, Petry H (2014) Safety profile of recombinant adeno-associated viral vectors: focus on alipogene tiparvovec (Glybera®). Expert review of clinical pharmacology 7(1): 53–65. doi: 10.1586/17512433.2014.852065
9. Tanner K, Kirchhof P, Schulenburg MGv et al. (2016) Genomanalysen als Informationseingriff. Ethische, juristische und ökonomische Analysen zum prädiktiven Potential der Genomsequenzierung, 1. Auflage. Schriften des Marsilius-Kollegs, Band 15. Universitätsverlag Winter GmbH Heidelberg, Heidelberg, Neckar
10. O'Daniel JM (2010) The prospect of genome-guided preventive medicine: a need and opportunity for genetic counselors. Journal of genetic counseling 19(4): 315–327. doi: 10.1007/s10897-010-9302-4
11. European Board of Medical Genetics (2010) Professional and educational standards for genetic counsellors in Europe. https://www.eshg.org/fileadmin/eshg/committees/EBMG/EBMGProfessionalAndEducationalStandardsForGeneticCounsellors-July2010.pdf
12. Bundeszentrale für politische Bildung (2002) Vom genetischen Wissen zum sozialen Risiko: Gendiagnostik als Instrument der Biopolitik. http://www.bpb.de/apuz/26176/vom-genetischen-wissen-zum-sozialen-risiko-gendiagnostik-als-instrument-der-biopolitik?p=all
13. Hubbard R (1993) Predictive genetics and the construction of the healthy ill. Suffolk Univ Law Rev 27(4), S. 1209-1224
14. Zerres K (2003) Humangenetische Beratung. Dtsch Arztebl(A 2720–2727 [Heft 42])
15. Concert Genetics (2017) The Current Landscape of Genetic Testing. https://www.concertgenetics.com/wp-content/uploads/2017/05/10_ConcertGenetics_CurrentLandscapeofGeneticTesting_2017Update.pdf
16. Balobaid A, Qari A, Al-Zaidan H (2016) Genetic counselors' scope of practice and challenges in genetic counseling services in Saudi Arabia. International Journal of Pediatrics and Adolescent Medicine 3(1): 1–6. doi: 10.1016/j.ijpam.2015.12.002
17. Weil J (2002) Genetic counselling in the era of genomic medicine. As we move towards personalized medicine, it becomes more important to help patients understand genetic tests and make complex decisions about their health. EMBO reports 3(7): 590–593. doi: 10.1093/embo-reports/kvf144

18. Plöthner M, Frank M, Graf von der Schulenburg J-M (2017) Ganzgenomsequenzierung in der deutschen Versorgung. Ökonomische Auswirkungen eines Einsatzes in ausgewählten Anwendungsgebieten (Whole-genome sequencing in German clinical practice : Economic impacts of its use in selected areas of application). Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 60(2): 143–150. doi: 10.1007/s00103-016-2492-7
19. Bundesärztekammer (2015) Ärztestatisitk 2015 - Ärztinnen nach Bezeichnung und Tätigkeitsarten. http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/Statistik2015/Stat15Tab04.pdf
20. Infodienst Öffentlicher Dienst (2018) TV-Ärzte - Ärzte an Universitätskliniken. http://oeffentlicher-dienst.info/aerzte/uniklinik/
21. Plöthner M, Frank M, Schulenburg J-MG von der (2017) Cost analysis of whole genome sequencing in German clinical practice. The European journal of health economics : HEPAC : health economics in prevention and care 18(5): 623–633. doi: 10.1007/s10198-016-0815-0
22. Statistisches Bundesamt (2018) Statistiken zur Bevölkerung in Deutschland. https://de.statista.com/themen/27/bevoelkerung/
23. Middleton A, Marks P, Bruce A et al. (2017) The role of genetic counsellors in genomic healthcare in the United Kingdom: a statement by the Association of Genetic Nurses and Counsellors. European journal of human genetics : EJHG 25(6): 659–661. doi: 10.1038/ejhg.2017.28
24. Hoskovec JM, Bennett RL, Carey ME et al. (2018) Projecting the Supply and Demand for Certified Genetic Counselors: a Workforce Study. Journal of genetic counseling 27(1): 16–20. doi: 10.1007/s10897-017-0158-8
25. Gendiagnostik-Kommission (2011) Richtlinie der Gendiagnostik-Kommission (GEKO) über die Anforderungen an die Qualifikation zur und Inhalte der genetischen Beratung gemäß 23 Abs. 2 Nr. 2a und 23 Abs. 2 Nr. 3 GenDG. In der Fassung vom 01.07.2011, veröffentlicht und in Kraft getretenam 11.07.2011 (Guideline of the Genetic Diagnosis Commission (GEKO) for requirements of the qualification for and contents of genetic counseling in accordance with paragraph 23 Abs. 2 No. 2a and 23 Abs. 2 No. 3 GenDg.The 1 July 2011 version released and implemented 11 July 2011). Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 54(11): 1248–1256. doi: 10.1007/s00103-011-1357-3
26. Patch C, Middleton A (2018) Genetic counselling in the era of genomic medicine. British medical bulletin. doi: 10.1093/bmb/ldy008
27. Shelton CA, Whitcomb DC (2015) Evolving Roles for Physicians and Genetic Counselors in Managing Complex Genetic Disorders. Clinical and translational gastroenterology 6: e124. doi: 10.1038/ctg.2015.46
28. Bennette CS, Gallego CJ, Burke W, Jarvik GP, Veenstra DL (2015) The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Genetics in medicine : official journal of the American College of Medical Genetics 17(7): 587–595. doi: 10.1038/gim.2014.156
29. Petersen B-S, Fredrich B, Hoeppner MP, Ellinghaus D, Franke A (2017) Opportunities and challenges of whole-genome and -exome sequencing. BMC genetics 18(1): 14. doi: 10.1186/s12863-017-0479-5
30. Myers RH (2004) Huntington's disease genetics. NeuroRx : the journal of the American Society for Experimental NeuroTherapeutics 1(2): 255–262. doi: 10.1602/neurorx.1.2.255
31. Gilbert-Diamond D, Moore JH (2011) Analysis of gene-gene interactions. Current protocols in human genetics Chapter 1: Unit1.14. doi: 10.1002/0471142905.hg0114s70
32. Rebelo S, da Cruz E Silva EF, da Cruz E Silva OAB (2015) Genetic mutations strengthen functional association of LAP1 with DYT1 dystonia and muscular dystrophy. Mutation research. Reviews in mutation research 766: 42–47. doi: 10.1016/j.mrrev.2015.07.004
33. El-Brolosy MA, Stainier DYR (2017) Genetic compensation: A phenomenon in search of mechanisms. PLoS genetics 13(7): e1006780. doi: 10.1371/journal.pgen.1006780
34. Miko I (2008) Phenotype variability: penetrance and expressivity. Nature Education 1(1):137

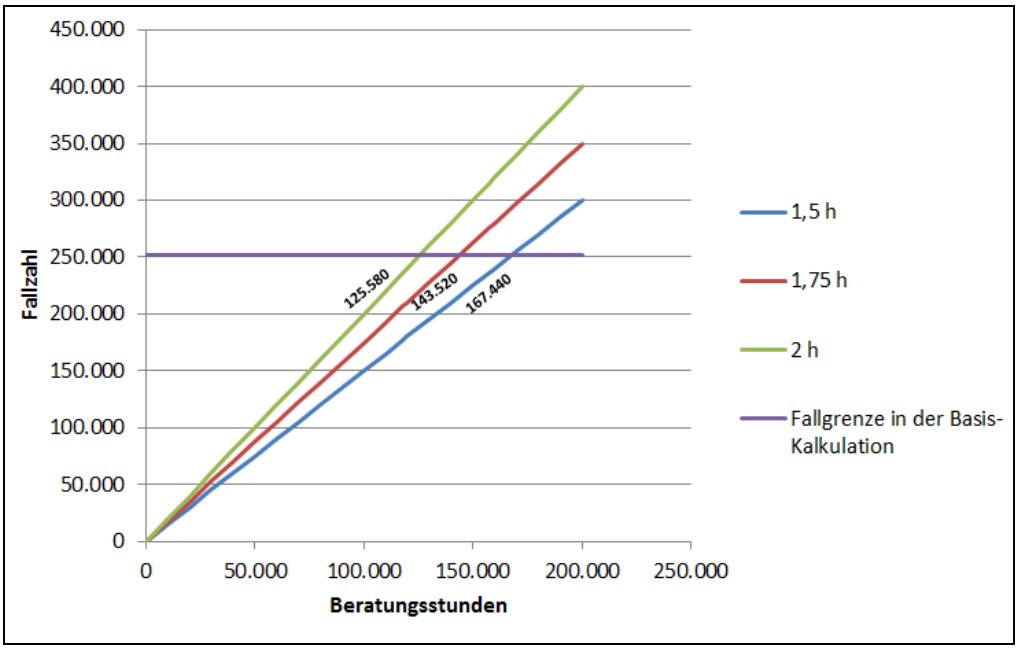
35. Burke W (2014) Genetic tests: clinical validity and clinical utility. Current protocols in human genetics 81: 9.15.1-8. doi: 10.1002/0471142905.hg0915s81
36. Deutsche Gesellschaft für Humangenetik e.V Fachgebundene Genetische Beratung – 72 Std. Kurs –. https://www.gfhev.de/de/Fachgebundene_Genetische_Beratung.htm
37. Vermeulen E, Henneman L, van El CG, Cornel MC (2014) Public attitudes towards preventive genomics and personal interest in genetic testing to prevent disease: a survey study. European journal of public health 24(5): 768–775. doi: 10.1093/eurpub/ckt143.
38. Wilde A, Meiser B, Mitchell PB, Hadzi-Pavlovic D, Schofield PR (2011) Community interest in predictive genetic testing for susceptibility to major depressive disorder in a large national sample. Psychological medicine 41(8): 1605–1613. doi: 10.1017/S0033291710002394.
39. Wade CH, Elliott KR (2017) Preferences for the provision of whole genome sequencing services among young adults. PloS one 12(3): e0174131. doi: 10.1371/journal.pone.0174131
40. Dodson DS, Goldenberg AJ, Davis MM, Singer DC, Tarini BA (2015) Parent and public interest in whole-genome sequencing. Public health genomics 18(3): 151–159. doi: 10.1159/000375115
41. Schmidtke, J., Rüping, U. (110(25): A-1248 / B-1090 / C-1082) Genetische Beratung: Nichtärztliche Personen können ein Gewinn sein. Dtsch Arztebl 2013
42. Cordier C, Lambert D, Voelckel M-A, Hosterey-Ugander U, Skirton H (2012) A profile of the genetic counsellor and genetic nurse profession in European countries. Journal of community genetics 3(1): 19–24. doi: 10.1007/s12687-011-0073-x
43. Skirton H, Kerzin-Storrar L, Patch C et al. (2003) Genetic counsellors: a registration system to assure competence in practice in the United kingdom. Community genetics 6(3): 182–183. doi: 10.1159/000078167
44. Godard B, Kääriäinen H, Kristoffersson U, Tranebjaerg L, Coviello D, Aymé S (2003) Provision of genetic services in Europe: current practices and issues. European journal of human genetics : EJHG 11 Suppl 2: S13-48. doi: 10.1038/sj.ejhg.5201111
45. Wissenschaftliches Institut der AOK (WIdO) Ärzteatlas 2017 - Daten zur Versorgungsdichte von Vertragsärtzen. https://www.wido.de/fileadmin/wido/downloads/pdf_ambulaten_versorg/wido_amb_pubaezteatlas2017_1117.pdf
46. Ärztezeitung (Hrsg.) (2015) KV finanziert Medizinstudium. https://www.aerztezeitung.de/politik_gesellschaft/berufspolitik/article/883314/sachsen-anhalt-kv-finanziert-medizinstudium.html
47. Association of Genetic Nurses and Counsellors (AGNC) (2016) Training to become a Genetic Counsellor. http://www.agnc.org.uk/about-us/training-to-become-a-genetic-counsellor/
48. American Board of Genetic Counseling (2018) Mission statement, purpose and values. https://www.abgc.net/about-abgc/mission-history/
49. Dobson und DaVanzo (2016) Projecting the supply and demand for certified genetic counselors: A workforce study. https://customer.abgc.net/app_themes/abgc_custom/documents/Dobson-DaVanzo-Report-to-NSGC_Final-Report-9-6-16.pdf
50. Salisbury M (2018) Counselor Shortage Threatens Genome-based Diagnostics. https://techonomy.com/2018/04/counselor-shortage-threatens-genome-based-diagnostics/

Tabellen und Abbildungen

Tabelle 1: Kapazitätsanalyse für humangenetische Beratungen

Jährliche Arbeitszeit in h (46 Wochen)	Anteil der Arbeitszeit an Beratungen (in %)	Jährliche Beratungsstunden (Kapazität in h)	
		Setting	
		Ambulant-tätige Fachärzte (n=135)	Stationär-tätige Fachärzte (n=55)
1.932	100	260.820	106.260
1.739	90	234.738	95.634
1.546	80*	208.656*	85.008
1.352	70	182.574	74.382
1.159	60	156.492	63.756
966	50	130.410	53.130
773	40*	104.328	42.504*
580	30	78.246	31.878
386	20	52.164	21.252
193	10	26.082	10.626
Anzahl Beratungsstunden Base Case (*)			251.160
Fallzahl (1,75 h/ Beratung)			**143.520**

Abbildung 1: Sensitivitätsanalyse der Fallzahlen in Abhängigkeit der Beratungsdauer



Modul 9

Health-Related Genetic Direct-to-Consumer-Tests in the German Setting: The Available Offer and the Potential Implications for a Solidary Financed Health-Care System

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Health-Related Genetic Direct-to-Consumer Tests in the German Setting: The Available Offer and the Potential Implications for a Solidarily Financed Health-Care System

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Keywords
Direct-to-consumer genetic testing · Health-related offer · Germany · Health-care system

Abstract
Background: The global genetic direct-to-consumer (DTC) market will reach a volume of USD 230 billion in 2018. The expenditures for this genetic analysis are borne by the customer, whereas consequential costs may arise for a solidarily financed system. In a first step, it is essential to gain an overview of the currently available offer in the German setting. ***Methods:*** In April 2016, we conducted a systematic internet search in the Google search engine. In November 2016, we updated the information of the webpages in terms of country, language, types of health-related tests, additional offer of non-health-related DTC test, information about sensitivity and specificity, certification and accreditation, costs as well as reference to German Act on Genetic Testing. ***Results:*** Thirty-five webpages were included in the final overview. A plurality of different predictive analysis options was identified. Price information was not available for all offered genetic analyses. Costs for predictive analysis in one disease vary between EUR 90 and 990, for predictive package analysis between EUR 232.18 and 375, and for genetic lifestyle analysis between EUR 84.55 and 570.20. ***Conclusions:*** Genetic results may lead to uncertainty and anxiety; therefore, subsequent costs for a solidarily financed system may arise. Genetic DTC tests may have an influence on different players on the micro-, meso- and macro-levels, which may have a cost-cutting or cost-increasing effect on health-care expenditures. The increased interest in genetic analysis as well as the possibility of worldwide internet-based access to genetic tests requires population-wide education.

Introduction

The community is characterized by an increased health consciousness [1]. Patients are becoming increasingly responsible and informed and also want to take a proactive role in their health-care management [2]. Besides the traditional health-care sector (e.g., medical services by physicians), citizens are using additional sources for getting health information [3]. For this purpose, the internet constitutes an essential tool for health information access [4]. Health information is thus easily available from home and the-so called "Dr Google" is often the primary source for health-related questions [5].

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In the genomic century, the knowledge of health-influencing genetic factors is steadily increasing [6]. The two main factors for the growing genetic knowledge are: First, progress in genetic technology, which is characterized by cheaper and faster genetic analysis [7]; and second, increased genomic knowledge as a result of genome wide-association studies (GWAS). GWAS enable a better understanding of genotype and phenotype correlations and also provide information about the probability for the development of specific diseases [8–10]. Hence, genetic information can be used for diagnosis, prognosis, and treatment [11] as well as for a "genome-guided preventive medicine" [12]. Based on the known associations between genetics and common diseases, the demand for genetic analysis has increased, particularly with a preventive approach [13].

In Germany, preventive or predictive genetic analyses without a direct and specific indication or only for interested people are basically not part of the standard benefit of the statutory health insurance. As a result, such genetic analyses can be accessed through case-by-case decision (e.g., predictive analysis for the risk of breast cancer due to the family history) or private payment. Besides the traditional market, an internet-based market – the so called direct-to-consumer (DTC) market – has been developed. The development of this market has been encouraged by a lower price, no geographic restriction, as well as the easy availability from home [14, 15]. Estimates suggest that the global genetic DTC market will reach a volume of USD 230 billion in 2018 [16]. DTC genetic tests are directly addressed to customers via television, print advertisements, or the internet [17]. Customers receive a test kit and send a sample (mostly saliva) back to the company. After analyzing the genetic material in their own or an outsourced laboratory, the information about the personal genetic makeup will subsequently be sent to the customers [18].

Overall, genetic DTC tests can be differentiated into health-related and non-health-related tests. Tests for identity (e.g., paternity and ancestry) can be classified as non-health-related DTC tests, whereas diagnostic and predictive tests (risk of disease) as well as lifestyle tests (nutrition, aging, behavior, etc.) can be classified as health-related tests [19–21]. In contrast to predictive or diagnostic genetic tests, lifestyle tests can be attributed a lower clinical value [21]. Therefore, the German Act on Genetic Testing (GenDG) heavily regulates the execution of genetic analysis with a predictive or diagnostic approach, which makes the integration of a physician necessary. However, this law is only obligated for companies located in Germany, and the access to offers of companies located in other countries is not restricted. According to the increased demand for genetic analysis [22] and the associated increasing use of predictive and therapeutic measures, it is important to analyze which kinds of genetic analysis the population is confronted with. In general, the costs for the execution of a genetic DTC test are borne by the customers, whereas follow-up costs may arise in the solidarily financed system. An informed patient develops other priorities, and this may have an influence on the different players in the health-care system. For this purpose, we conducted a systematic internet analysis to identify the currently available health-related genetic DTC offers in the German setting. Therefore, the review had the following objectives: (1) to identify the offer of health-related genetic DTC tests in the German setting; (2) to highlight and discuss the implications of genetic DTC tests for a solidarily financed health-care system

Methods

First, review elements (objective/aim, inclusion and exclusion criteria, and outcomes) were defined in order to focus on the scientific issue and facilitate the internet search (Table 1).

In April 2016, we conducted a systematic internet search using the Google search engine. To generate the maximum number of heterogeneous hits, we deactivated the installed adblocker as well as the standard activated web protocol. For the search strategy, we used single and combined terms in the German language. For single terms, we used different common German terms for genetic analysis and combined the most common with genetic DTC test-specific terms. Accordingly, the following search strategies were used: (1) genetic analysis, (2) genetic test, (3) genetics test, (4) genetic testing, (5) DNS testing, (6) DNA analysis, (7) genetics analysis, (8) DNA testing, (9) DNS analysis, (10) genetic analysis, (11) DNS test, (12) DNA test, (13) genetic test, (14) genetic analysis AND diseases, (15) genetic analysis AND lifestyle, (16) genetic analysis AND health, (17) genetic analysis AND private, (18) genetic analysis AND at home, (19) genetic analysis AND cancer, (20) DNS test AND diseases, (21) DNS test AND lifestyle, (22) DNS test AND health, (23) DNS test AND private, (24) DNS test AND at home, (25) DNS test AND cancer, (26) DNA test AND diseases, (27) DNA test AND lifestyle, (28) DNA test AND health, (29) DNA test AND private, (30) DNA test AND at home, (31) DNS test AND cancer, (32) genetic test AND diseases, (33) genetic test AND lifestyle, (34) genetic test AND health, (35) genetic test AND private, (36) genetic test AND at home, (37) genetic test AND cancer.

The systematic internet search was performed independently on two computers. Furthermore, the assessment of the webpages was also conducted independently by 2 researchers. Disagreements were resolved through discussion. Criteria for inclusion were as follows: (1) webpages offering a health-related genetic DTC test (diagnostic and predictive tests as well as lifestyle-tests); (2) tests were primarily targeted at customers (not physicians or

Table 1. Review objective

Objective/aim	To point out the available offer of health-related genetic DTC tests; highlight the potential implications of health-related genetic DTC tests for a solidarily financed health-care system
Inclusion criteria	Webpages that offer health-related genetic DTC tests (predictive and diagnostic tests as well as lifestyle tests; webpages were not restricted to specific predictive/diagnostic analysis or lifestyle tests or registered offices and languages; tests were targeted at customers; direct selling webpages
Outcomes	Type of tests and costs; further comparative aspects (registered offices, languages, additional supplement of non-health-related tests, information about sensitivity and specificity, reference to GenDG and information about certification and/or accreditation)

other medical providers); and (3) direct selling webpages (webpages only with test links or advertisements were not included) (see Table 1). In the course of an update in November 2016, offers and the provided information in the webpages were actualized. The included webpages were not restricted to countries, languages, and specific types of genetic analysis. To ensure comparability, the costs were converted to EUR at the exchange rate of the current year [23].

Results

The systematic internet search retrieved 11,199 webpages. After screening for eligibility, 35 webpages were included in the final overview (Fig. 1).

The webpages are characterized by a variety of aspects, such as country, language, types of health-related tests, cost of the specific tests, information about sensitivity and specificity, information about certification and accreditation, as well as information about the availability of and additional supplement of non-health-related tests. A detailed overview is provided in Table 1.

Country and Language

The majority of included webpages (17×) have their headquarters located in Germany, followed by Switzerland (3×) and Slovenia (3×). Overall, 12 different countries were identified as company headquarters. Twelve of the included webpages present their offer only in German, whereas 8 of these are German companies and 4 are foreign companies. One company provides a translation service, whereby a variety of languages is available. Furthermore, one company provides a direct selection of 11 languages. Five of the included webpages provide no German translation, whereas 4 of these are only represented in English.

Offer of Health-Related DTC Tests

Eleven webpages offer only genetic lifestyle tests and 16 webpages offer only predictive or diagnostic genetic DTC tests. An offer of genetic lifestyle DTC tests as well as predictive and diagnostic genetic DTC was identified on 8 webpages. Of the 17 webpages with their headquarters located in Germany, 5 offer genetic lifestyle tests, 8 predictive and diagnostic DTC tests, and 4 both types of genetic analysis. The offer of the 8 webpages represents one genetic analysis in the diagnostic content (lactose intolerance gene mutation analysis) and 7 genetic analyses in the predictive content (prenatal test [3×], tests of therapeutic safety and tests of genetic disease dispositions [3×]).

Generally, in terms of predictive analysis, a plurality of genetic analyses were identified for general diseases (type 1 and 2 diabetes, migraine etc.), immune system (lupus, multiple sclerosis etc.), aging (Alzheimer disease, osteoporosis, etc.), cancer dispositions (bladder, breast, prostate, colon, etc.), and pharmacogenetic testing (antidepressants, oncology products, etc.). Thereby, customers have the possibility to choose between predictive analyses especially for single diseases (8×) or purchase a package with an analysis of different genetic dispositions (9×). Four providers offer a mixed range of single and/or package analysis. For example, in terms of prenatal analysis, some offers provide a choice between a single analysis of trisomy 21 or trisomy 21, 18, and 13; additionally with sex determination, chromosomal abnormality, and/or sex chromosomal disorders. Some providers offer a package of genetic analyses for up to 35 diseases, gender-specific analysis, and an additional analysis of pharmacogenetics effects (partly up to 230 drugs). Genetic lifestyle DTC tests for weight, nutrition, and fitness are represented by a variety of different

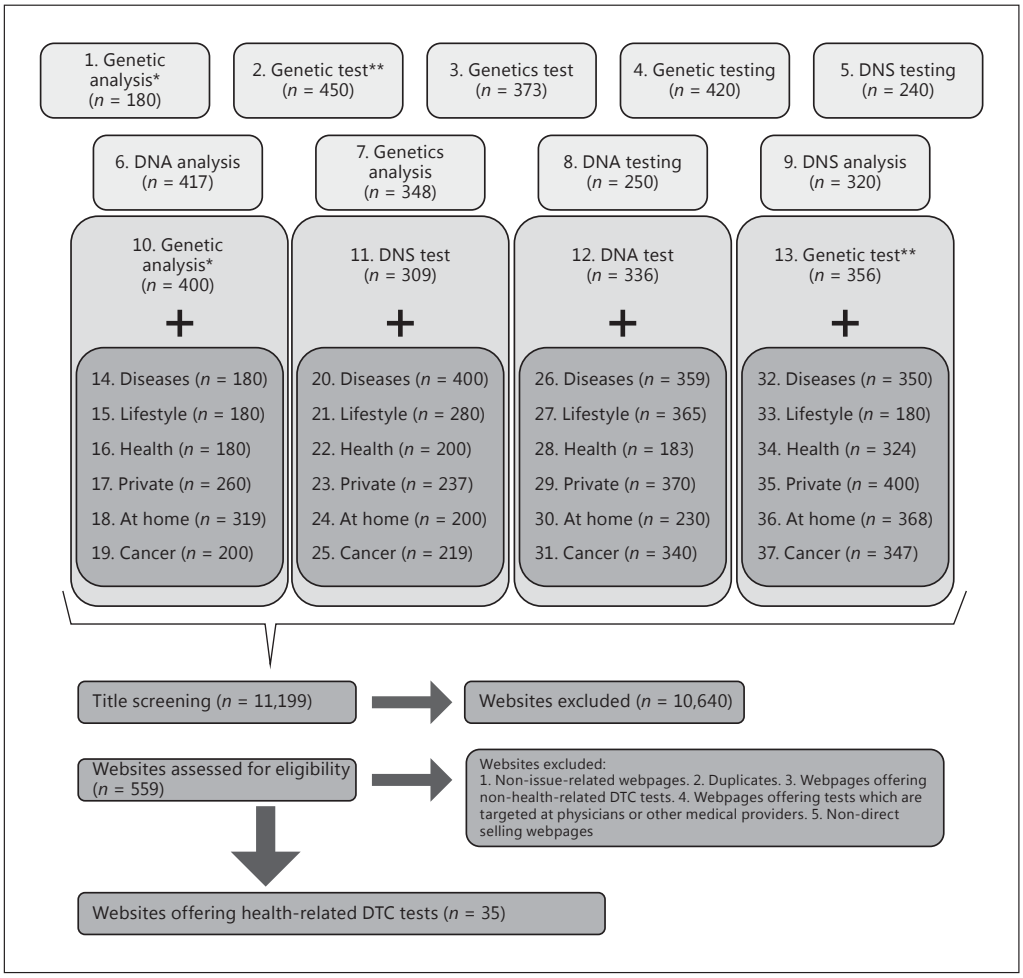

Fig. 1. Flow diagram of websites identified on the basis of inclusion criteria. */**, two different search terms in the German language; *n*, number of displayed hits.

terms (e.g., gene-weight analysis, metabolic analysis, nutrigenetic analysis, fitness). Some bundled offers provide an analysis in areas of weight, nutrition, and fitness, and others focus only on one area. Moreover, genetic analysis for hair loss, body height, day or night person, memory performance, etc. was also identified. Furthermore, the majority of the included providers focus only on health-related analysis. Only 6 webpages provide an additional supplement of non-health-related genetic DTC test (paternity test, test for relationship etc.).

Costs of Predictive and Diagnostic Genetic DTC Tests

Most of the companies (20×) provide price information for all offered analyses. However, the webpages of 10 companies do not communicate any price information. Three companies provide price information only for a few analyses. Two webpages directly refer price information on request online or by physician or hotline. There is a wide variety of prices. The cost for predictive single analysis can vary between EUR 89 (e.g., test for risk of thrombosis) and EUR 990 (e.g., test for risk of dystrophy or test for risk of metabolic disease). The cost for predictive package analysis varies between EUR 232.18 (test of

risk for 34 different diseases) and EUR 375 (test of risk for 28 common diseases). The identified prices for pharmacogenetic testing range between EUR 160.88 (test for therapeutic safety of clopidogrel) and EUR 395.49 (test for therapeutic safety of antidepressants). Cost differences of EUR 220 and 395.49 for an efficacy test of tamoxifen were identified. In the diagnostic content, especially in terms of genetic analysis for dietary intolerances, costs between EUR 69 (e.g., lactose) and EUR 700 (e.g., food intolerances) were found. Prices for prenatal testing vary according to the extent of genetic analysis (e.g., trisomy 21 or trisomy 21, 18, 13) and partly on the processing time. Hence, prices are between EUR 249 and 649.42.

Costs of Lifestyle-Related Testing

The cost for genetic lifestyle analysis varies between EUR 84.55 (analysis for obesity and overweight) and EUR 570.20 (genetic weight analysis).

Additional Information

Six webpages provide information about sensitivity and/or specificity. Five of these are located in Germany and one in Canada. Another provider advertises regarding "highest accuracy" [32]. All of these are offers in a predictive or diagnostic context. Of all 35 webpages included, 10 provide some information about the GenDG. All of these, except one, are located in Germany. All except 14 provide information about certification and/or accreditation. The majority of these are located in Germany.

Discussion

This comprehensive review presents an overview about the current available health-related genetic DTC tests in the German setting. It shows that a variety of health-related but also non-health-related DTC tests exist. The offer of health-related genetic DTC tests is represented by lifestyle tests as well as predictive and diagnostic tests. According to the GenDG, predictive and diagnostic genetic tests are restricted to physicians, whereas predictive tests may only be performed by human geneticists. However, some companies created possibilities to offer genetic tests while meeting the conditions of the GenDG. Examples of these identified methods are as follows. (1) The execution of the genetic analysis (laboratory process) will only be performed after a genetic counselling and with the signature of a qualified physician [31], or the genetic test can only be ordered by or with a physician, and afterwards the results are transmitted to the physician. (2) Companies additionally provide the possibility of genetic counselling by their own physician [35]. Therefore, the properties of a genetic DTC test in a strict sense (order, saliva sample, and receipt of results at home) are not fulfilled by such access methods. However, the offer is directly addressed to the customer, and the additional integration of physicians for German-located companies could be a possibility to conform to the GenDG.

The GenDG is an act that highly restricts access to genetic analysis. However, in Europe there are no common regulations for genetic analyses, and therefore also not for DTC tests. Borry et al. [59] provide an overview about the different regulations for genetic analyses in 7 European countries (Belgium, Germany, France, the Netherlands, Portugal, Switzerland, and UK). This report shows that none of these countries has specific regulations for genetic DTC testing. Rather, it is a transfer of the existing legislation to the DTC context. In some of these countries (France, Germany, the Netherlands, Portugal, and Switzerland), genetic analyses are restricted to physicians, and genetic counselling is obligatory. Due to the fact of missing European regulations and the unlimited access to various international genetic DTC offers, some organizations and agencies (for example, Initiative of European Academies Science Advisory Council [EASAC] and the Federation of European Academies of Medicine [FEAM] [60] or the Human Genetics Commission [61]) published statements for information and education about DTC genetic testing.

This market analysis provides an overview of the existing variety of health-related genetic testing (genetic predictive or diagnostic tests as well as lifestyle analysis) in the German setting. The supplement is characterized by a plurality of aspects, which makes a comparison for customers difficult. In the context of lifestyle analysis, interested people are faced with different terms, extensions of analysis as well as prices. In the predictive context, people have to decide between analysis for one specific disease and a package analysis. Costs for single analysis are partly more expensive than those for comprehensive analysis. Moreover, information about the amount of investigated gene variations may be difficult for costumers to evaluate [62]. Furthermore, tests and costs for a specific indication, for example the risk of thrombosis (Table 2) are not or hardly comparable for customers. Test cost varies with the analysis of the specific targets. However, mostly there is no information about it, and this shows a lack of transparency for interested people.

Table 2. Overview of included webpages

General information			Offer			Additional information		
company	registered office	languages	health-related tests	costs	non-health-related tests	sensitivity or specificity/ accuracy	reference to GenDG	certification and/or accreditation
Abnehmgene [24]	Spain	German	Gene-weight analysis	EUR 398/419[1]	No	ns	ns	Yes
Adison Lab[2] [25]	Ireland	Spanish, English, French, German, Italian, Russian, Romanian	Genetic analyses of food intolerances	EUR 700	No	ns	ns	ns
Amway [26]	Germany	German, English, Turkish, Russian	Weight	EUR 570.20	No	ns	ns	ns
Ceneta [27]	Germany	German, English, Turkish	Trisomy 21, 18, 13, and sex chromosomal disorders and XY chromosomal disorder (as required for sex determination)	EUR 299	No	Yes	Yes	ns
			Trisomy 21, 18, 13 (as required sex determination)	EUR 299				
			Trisomy 21 (as required sex determination)	EUR 249				
Coloalert [28]	Germany	German	Colon cancer prevention test	EUR 98.50	No	Yes	ns	Yes
DNAdirekt [29]	The Netherlands	German	Risk of thrombosis	EUR 99	Yes	ns	ns	Yes
			Risk of hemochromatosis	EUR 99				
			Prader-Willi syndrome	ns				
			Apo-E Alzheimer disease	EUR 99				
DNAFit [30]	UK	English	Diet (diet type, carbohydrates response, saturated fat response, lactose intolerance) (different packages: core info or more than core info or all information)	EUR 119–239	No	ns	ns	ns
			Fitness (different packages: core info: power endurance response, sports injury resilience, recovery speed, recovery nutrition needs) or all information (aerobic [$VO_{2\ Max}$] potential, fitness genotype breakdown)	EUR 145–179				
			Diet and fitness	EUR 338				
DNA Plus-Zentrum für Humangenetik [31]	Germany	German, English (UK and US), Hungarian	Nutrition (dietary, weight); digestion (lactose, gluten, colon); metabolism (iron, diabetes, Alzheimer, detoxification); movement (sport, joints, bones); pharma (drugs, remuneration, hormone replacement); eyes (glaucoma, macula); heart (thrombosis, heartbeat, blood pressure, artery); beauty (hair loss male and female, periodontitis); trainees (pregnancy, baby100+); cancer (prostate, breast); allergy	ns	No	ns	Yes	ns
DTC DNATesting Center [32]	Austria	German	Risk of heart attack	EUR 890	Yes	ns[3]	Yes[4]	Yes
			Risk of cancer	EUR 790				
			Risk of diabetes	EUR 290				
			Risk of stroke	EUR 640				
			Risk of osteoporosis	EUR 490				
			Point of aging	EUR 990				
			Risk of cystic fibrosis	EUR 890				
			Risk of anemia	EUR 790				
			Risk of dystrophy	EUR 990				
			Risk of metabolic disease	EUR 990				

Table 2 (continued)

General information			Offer			Additional information		
company	registered office	languages	health-related tests	costs	non-health-related tests	sensitivity or specificity/ accuracy	reference to GenDG	certification and/or accreditation
DNAnutri Control [33]	Austria	English, German	Weight sensor	ns	No	ns	Yes	Yes
			Nutrition sensor	ns				
			Sport sensor	ns				
DNA Weight Control [34]	Switzerland	German, English	Genetic metabolic analysis	ns	No	ns	ns	ns
Dr. Seibt Genomics [35]	Germany	German, English	Several tests for: DNA and diseases (alpha-1-antitrypsin-deficiency, Alzheimer, atherosclerosis risk, caffeine, Gilbert syndrome, hereditary hemochromatosis, histamine intolerance, hyperlipoproteinemia, lactose intolerance, Bekhterev's disease, Crohn's disease, periodontitis risk, risk of thrombosis (factor 2, factor 5, PAI-1, MTHFR), celiac disease; panel-analyses: adiposity, Alzheimer disease/dementia, BRCA1&2, BRCA1&2 ovarian carcinoma, cardiologic analysis, dermatologic analysis, metabolism of drugs and exogenous substances, type 2 diabetes, hereditary disease, estrogen-specific analysis, glaucoma, health, capsule fibrosis, cancer hotspot, macula, osteoporosis, pharmacogenomics, prostate, starter); DSG-combi: three different,	price on request	No	ns	Yes	ns
			DSG sequencing: WES, WGS					
			Liquid biopsy marker: 23 different; liquid biopsy panel and liquid biopsy exome					
			Pharmacogenetics tests: antidepressants (13 different); atypical neuroleptics, beta-blockers, oncological (9 different), opiates, proton pump inhibitor (2 different), statins, thrombocyte aggregation inhibitors; DSG-combi analysis (5 different); drug interaction check					
EasyDNA [36]	Switzerland	German, English, French	Analysis includes: cancer predisposition (bladder, breast, colon, stomach, lung, prostate, skin), general (overweight, migraine, type 1 and 2 diabetes), aging (Alzheimer disease, osteoarthritis, rheumatoid arthritis), cardiovascular events (aneurysm, atrial fibrillation, venous thromboembolism, peripheral arterial occlusive disease, heart diseases); immune system (lupus, Graves' disease, celiac disease, multiple sclerosis, psoriasis)	CHF 375 (EUR 347.01)	No	ns	ns	Yes
FutureGenetic [37]	Canada	German, English	Test includes 28 of the most common diseases: age-related macular degeneration, alopecia, Alzheimer disease, atrial fibrillation, basal cell carcinoma, bladder cancer, breast cancer, celiac disease, colon cancer, coronary heart disease, exfoliations glaucoma, stomach cancer, Graves' disease, intracerebral aneurysm, lung cancer, lupus, melanoma, migraine, multiple sclerosis, obesity, open-angle glaucoma, peripheral arterial occlusive disease, prostate cancer, psoriasis, rheumatoid arthritis, type 1 and 2 diabetes, venous thromboembolism	EUR 375	No	ns	ns	Yes

Table 2 (continued)

General information			Offer			Additional information		
company	registered office	languages	health-related tests	costs	non-health-related tests	sensitivity or specificity/ accuracy	reference to GenDG	certification and/or accreditation
Genetic balance [38]	Germany	German	Genetic balance (diet, weight, nutrition) basic package[5]	EUR 399.00	No	ns	Yes	Yes
			Genetic balance (diet, weight, nutrition) medium package[5]	EUR 419.00				
			Genetic balance (diet, weight, nutrition) premium package[5]	EUR 449				
			Health control – cardiovascular diseases	ns				
			Health control – metabolism	ns				
			Health control – bone health	ns				
			Health control – eye health	ns				
			Health control – Alzheimer disease and prevention	ns				
Genoris [39]	Italy	Italian, German	DNA and weight	ns	No	ns	ns	Yes
			DNA and nutrition	ns				
			Premium plus sensor female/male: 35 different diseases/110 gene variations/effect or adverse events of 230 drugs	ns				
			Premium sensor female/male: 22 different diseases/90 gene variations/ adverse events of 230 drugs	ns				
			Female sensor:12 different diseases/65 gene variations/ adverse events of 73 drugs/assessment of risks and advantages of hormone replacement therapy (especially for women 40+)	ns				
			Male sensor: 65 gene variations, 12+ different diseases, adverse events of 73 drugs, assessment of risks and advantages of hormone replacement therapy, assessment the needs of minerals (male sensor 40+)	ns				
			Risk of breast cancer: 9 gene variations, genetic checkup program, adjustments in lifestyle, 13+ gene variations for the effect of 40 relevant drugs	ns				
			Primary prevention: 52 gene variations, more than 10 different diseases, effects and adverse events of 54 drugs	ns				
			Gastrointestinal sensor: 5 gene variations, 2 food intolerances, early detection of Crohn's disease	ns				
Geneplanet [40]	Slovenia	German, Slovenian, Croatian, English, Hungarian	Nutrigenetic analysis	EUR 399	No	ns	ns	Yes
coCap [41]	Germany	German, English	Metabolic analysis (3 analyses with different extension)	ca. EUR 330[6]	No	ns	ns	ns
Genovia [42]	Germany	A variety of translation options	Hormonal risk of thrombosis during pregnancy	EUR 89	Yes	ns	ns	Yes
			Risk of thrombosis	EUR 89				
			Test of drug intolerance	EUR 130				
			Test of tamoxifen intolerance	EUR 220				
			Macular degeneration	EUR 89				
			Lactose intolerance	EUR 89				
			Alcohol intolerance	EUR 84.55				
			Coffee intolerance	EUR 89				
			Obesity and overweight	EUR 84.55				

Table 2 (continued)

General information			Offer			Additional information		
company	registered office	languages	health-related tests	costs	non-health-related tests	sensitivity or specificity/ accuracy	reference to GenDG	certification and/or accreditation
Humatrix [43]	Germany	German	Therapeutic safety of antidepressants	EUR 395.49	Yes	Yes[4]	Yes[4]	Yes
			Therapeutic safety of clopidogrel	EUR 160.88				
			Therapeutic safety of statins	EUR 261.43				
			Therapeutic safety of contraceptives	ns				
			Therapeutic safety of tamoxifen	EUR 395.49				
Illid [44]	Germany	German	Metabolic analysis	EUR 300–400[7]	No	ns	ns	ns
Jenagen [45]	Germany	German	Lactose intolerance	EUR 69	Yes	ns	Yes	Yes
LifeCodexx [46]	Germany	German, English, French, Italian	Trisomy 21 and genetic sex determination	EUR 299	No	Yes	Yes	Yes
			Trisomy 21, 18, 13 and genetic sex determination	EUR 349				
			Trisomy 21, 18, 13, test of maldistribution of sex chromosome, genetic sex determination	EUR 399				
Lifegenetics [47]	Slovenia	English	DNA slim test (nutrition and metabolism and therefore, weight)	EUR 229	No	ns	ns	ns
			DNA test premium (health and prevention factors: alcohol metabolism, bone health, caffeine and nicotine metabolism, cardiovascular health, celiac disease, detoxification ability of your body; fat, sugar and insulin regulation, lactose intolerance, muscular potential and cramps)	EUR 279				
			DNA test premium + DNA test slim	EUR 299				
			DNA test baby (health and prevention factors: bone health, caffeine and nicotine metabolism, cardiovascular health, celiac disease, detoxification ability of your body; fats, sugar and insulin regulation, lactose intolerance, muscular potential and cramps)	EUR 279[8]				
Meinlabtest [48]	The Netherlands	German	Nutrigenetic analysis	EUR 399	No	ns	ns	Yes
			Gene analysis includes 19 different diseases: Alzheimer disease, asthma, arterial fibrillation, basal cell carcinoma, breast cancer, celiac cancer, colon carcinoma, diabetes type I and II, gallstones, glaucoma, heart attack, hypertension, lung cancer, multiple sclerosis, psoriasis, restless leg syndrome, rheumatoid arthritis, venous thromboembolism) and analysis of drug reactions (statins, omeprazole, clopidogrel, metformin, perindopril, warfarin) as well as analysis of character and talents (metabolic system, muscle structure, memory capacities, pain sensitivity, etc.)	EUR 499				
			Nutrigenetic analysis + personal gene	EUR 799				
MIADNA [49]	ns	English	Diet and nutrition (exercise potential, eating behavior, etc.)	USD149 (EUR 139.79)	no	ns	ns	ns
			Wellness and lifestyle (hair loss, learning, memory performance, etc.)	USD 119 (EUR 111.62)				
			Children's DNA discovery (body height, day or night person, athletic potential)	USD 119 (EUR 111.62)				

Table 2 (continued)

General information			Offer			Additional information		
company	registered office	languages	health-related tests	costs	non-health-related tests	sensitivity or specificity/ accuracy	reference to GenDG	certification and/or accreditation
Medical Rogaska [50]	Slovenia	English, German, Russian, Italian, Slovenian	Genetic analysis includes 13 diseases: arterial fibrillation, stroke, colon and rectum carcinoma, Crohn's disease, multiple sclerosis, hypertension, peripheral arterial disease, type 1 and 2 diabetes mellitus, skin cancer, rheumatoid arthritis, myocardial infarction, chronic kidney disease); for women additional test of risk of breast and ovarian cancer, for men additional test of risk of prostate and lung cancer	ns	No	/	/	Yes
			Extended genetic analysis includes 19 diseases: additional Alzheimer disease, leukemia, age-related degeneration, gallstones, asthma, celiac disease; for women additional test of risk of breast and ovarian cancer, for men additional test of risk of prostate and lung cancer	ns				
			Diet test includes 35 analyses for body weight, metabolism and health, vitamins and minerals, nutrition habits, metabolic efficiency, detoxification and antioxidants, sport and leisure time as well as dependencies and ageing; in total 110 gene variations	ns				
Nifty [51]	China	Chinese, Thai, Romanian, Korean, Bulgarian, Turkish, Russian, Polish, Slovenian, Arabic, English	Prenatal test of the most common trisomies (T21, T18, T22, T16, T9), deletion syndromes, sex chromosomal aneuploidy	price information by physician or hotline	No	Yes	ns	ns
Nutrilite [52]	Germany	German	Weight	ns	No	ns	ns	Yes
Oncotype [53]	Germany	German, English, French, Greek, Spanish, Portuguese, Japanese, Irish	Breast cancer test/21 gene expression test	ns	No	ns	ns	ns
Prenatalis [54]	Germany	German, English	Trisomy 21, 18, 13	EUR 427.94/ EUR 532.85[9]	No	Yes	Yes	Yes
			Trisomy 21, 18, 13, and gonosomal aberrations	EUR 544.85/ EUR 649.42[9]				
Primahome [55]	Switzerland	English, Italian	Celiac disease and/or lactose	ns	No	Yes	ns	Yes
Progenom [56]	Germany	German	Weight and nutrition	ns	No	ns	Yes	Yes
			Several tests for: breast health sensor; bone health sensor; toxicological sensor; thrombosis sensor; cardiovascular sensor; pharmacological sensor; AMD sensor; glaucoma sensor; diabetes sensor; hypertension sensor; gluten sensor; lactose sensor; IBD sensor; Alzheimer sensor; joint sensor; periodontitis sensor; HIV resistance sensor; iron sensor; ADHD sensor; female sensor pregnancy; female health sensor	ns				
			Sport sensor	ns				

Table 2 (continued)

General information			Offer			Additional information		
company	registered office	languages	health-related tests	costs	non-health-related tests	sensitivity or specificity/ accuracy	reference to GenDG	certification and/or accreditation
SkinDNA [57]	Germany	German	Several tests for: accelerate collagen degradation; reduced protection of glycation; impairment of UV skin protection; reduced protection for free radicals; increased risk of inflammation	ns	No	ns	ns	ns
Whozthedaddy [58]	Canada	English	Diet and nutrition	GBP 119 (EUR 138.86)	Yes	Yes[10]	ns	Yes
			Wellness and lifestyle	GBP 99 (EUR 115.47)				
			Children's DNA discovery	GBP 99 (EUR 115.47)				
			Predisposition test includes 34 different diseases; immune system: lupus, Graves' disease, celiac disease, multiple sclerosis, psoriasis; cardiovascular/cerebrovascular conditions: intracranial aneurysm, atrial fibrillation, heart disease, peripheral arterial disease, venous thromboembolism; aging: Alzheimer disease, rheumatoid arthritis, osteoporosis; general health: obesity, migraine, type 1 and 2 diabetes, alopecia, gallstones, sugar consumption, folate metabolism, vitamin B_6 metabolism, vitamin B_{12} metabolism, vitamin D metabolism; cancer: bladder, breast, colorectal, gastric, lung, prostate, skin, basal; ocular (eye) disorders: open-angle glaucoma, exfoliation glaucoma	GBP 199 (EUR 232.18)				
			Prenatal testing (13, 18, 21, X, Y)	GBP 399 (EUR 465.53)				

ns, no information was found. [1] Cost difference arising due to type of report of result (PDF or book). [2] The webpage in English is represented by more genetic tests (DNA test dermatological problems etc.). [3] Advertising with highest accuracy. [4] Only for paternity. [5] Different price occurs due to additional individualized receipt book or form of results report. [6] Price depends on the scope of analysis or service package. [7] Price depends on consulting service and duration. [8] Additional shipping costs (EUR 39 or EUR 12). [9] Price difference results due to duration (5 or 8–10 working days for transmission of results). [10] For prenatal testing.

Initially, we wanted to clarify why citizens would like to perform a health-related genetic analysis and which aspects attract them in this market model. In the population, health awareness is a growing issue [1, 63]. In connection with the ongoing reports of new genetic findings, curiosity and interest about health risks also increase [64, 65]. Vayena [66] investigated the reasons for undergoing genetic testing. However, receiving actionable health information was mentioned as least important, whereas curiosity was stated as the primary reason. This motivation is relieved by an easy access to a genetic analysis through the internet. Thereby, no geographical boundaries and distances from physicians affect the access [14]. Additionally, in most cases, predictive genetic analyses without a specific indication were not covered by German statutory health insurances. Hence, genetic analyses are often subject to private payments. For this purpose, genetic analysis via internet seems to be a less expensive alternative to traditional examination by physicians [67].

Generally, the genetic DTC market is an issue in the German setting, and the economic relevance for a solidarily financed health-care system has to be discussed. In the discussion of the potential benefits of health-related genetic analysis, a distinction between lifestyle tests and predictive/diagnostic analysis must be made. Whereas a lower medical value or influence is attributed to lifestyle tests, predictive genetic analyses could have considerable consequences for human health [68]. In recent years, sev-

eral studies investigated the influence of such health-related genetic analysis on health behavior of the tested person. In the literature, no ambiguous result could be identified. Bloss et al. [69], for example, evaluated the behavior of people after receiving health-related genetic information; no change in behavior with respect to anxiety and diet was determined. In contrast, Kaufman et al. [70] stated that after testing, one-third paid more attention to a healthy diet, 14% enhanced their physical activity, and 31% were more determined to exercise. Nonetheless, the strength of the effects on health behavior may depend on the type of analysis. Hence, genetic analysis focusing on lifestyle information has a minor effect on changing behavior than identified genetic mutations in a predictive context. In this context, the psychological burden of patients is a frequently discussed issue [71]. Genetic information could lead to fear of disease, depression, and fear of genetic discrimination [72, 73]. However, aside from these negative consequences, genetic information may also have a positive impact [74]. A reduction in disease-related anxiety may result from the exclusion of a disease, based on genetic analysis [75].

The aforementioned aspects may also have implications in a solidarily financed health-care system and influence the health-care budget. A genetic DTC analysis is performed independently and on the patient's own account. The genetic knowledge gained through the analysis may affect the expenditures on different levels (micro-, meso-, macro-level) of the health-care system. Thereby, patients and physicians are actors on the micro-level, insurances are actors on the meso-level, and the state or the system represents the actors on the macro-level. The effects of health-related genetic testing on the specific levels vary according to the type of the test (predictive/diagnostic or lifestyle). As previously mentioned, lifestyle analyses are attributed a lower impact on health. However, an independent prevention on the basis of the molecular genetic test and lifestyle changes (nutrition and sports) may reduce (private) illness-related subsequent costs for the *patients*. On the other hand, a lack of success (e.g., weight reduction) may lead to additional/increased use of services of the health-care system. Physicians are faced with more health-conscious and possibly healthier patients, and this may have a positive impact on prescriptive praxis and a number of regulations. An increased number of doctor consultations as well as increased costs of counselling resulting from lifestyle tests may negatively affect physicians on the micro-level. This may lead to an increase in expenses for insurances on the meso-level. However, such kinds of health-related tests may also be beneficial. An increase in the use of measures of primary prevention offered by the health insurance (fitness center, nutrition counselling) as well as more health-conscious insured parties may prospectively lead to cost reductions. These cost savings could be achieved by a reduction in subsequent illness-related costs and in the days where one is incapable of work. Overall, considered from the perspective of the *system or state*, these effects may lead on the one hand to a decrease in expenses for Statutory Health Insurance, and on the other hand to increased human capital caused by a more health-conscious population. Although a negative influence on the expenditure is estimated to be low, in contrast to the discussed lifestyle-tests, predictive genetic analysis may influence the overall health-care budget significantly. On the micro-level, after receiving predictive test results, positive as well as negative results may occur. The knowledge about the likelihood for one or a variety of specific diseases could induce measures of primary (e.g., precautionary measures, risk reduction) and secondary prevention (e.g., participation in early detection examinations, measures to prevent a manifestation) in the *customers*. In terms of drug application, genetic test results could lead to a reduction of adverse events. Genetic information may also have a negative effect on patients. This occurs primarily through overestimation of risks [68]. Interested people may become healthy sick people [76], who are characterized by anxiety, uncertainty, and psychological problems. Informed patients may develop other priorities, resulting in an increase of several services and a rise in demand for diagnostic clarifications. Furthermore, family members and, thus, potential risk carriers may become unsettled and increase their demand for medical services. Some of the few positive effects (targeted examination and treatment, close monitoring of risk patients, initiation of precautionary measures, and optimization of medicinal therapy) occur for physicians due to predictive knowledge and some cost-increasing aspects. As a result of uncertainty, patients may increase their demand for doctor consultations and also increase the expense of counselling. Due to the predictive findings, an additional or renewed diagnostic clarification is often necessary. Basically, predictive findings may encourage a demand-induced supply. Effects of the micro-level influence the effects as well the cost-situation for *insurances*. Early intervention options for risk patients may reduce follow-up costs in terms of avoiding disease manifestations, timely prevention, treatment, and reduce days where one is unable to work. Negative effects may result in costs for additional (partly unnecessary) medical services (e.g., costs to verify

results). Further issues in this context for insurances are indirect risk selection, migration of good risks to private insurance companies, increase of expenses, and thus an increase of additional contributions. Overall, this means a softening of the term "indication" for the system, which may lead to a service extension. The oversupply or misuse of results may increase expenses in a solidarily financed health-care system. However, on the other hand, predictive results may also have positive effects on the health-care budget as well as lead to improved cost-effectiveness of medical measures through targeted use.

In summary, positive and negative effects may occur due to genetic DTC tests for a solidarily financed health-care system. At the moment, a clear statement regarding the effects that will dominate can hardly be assessed. In a system with many chronic diseases, behavior changes or a more frequent use of medical check-ups may be beneficial [77]. However, this presumes that customers understand this genetic knowledge and are able to deal with deterministic results [78, 79]. German providers of predictive and diagnostic DTC tests have to ensure the integration of a physician and/or a genetic counselling for such analysis. Advised customers are more informed and are better able to deal with probabilistic results. Hence, the strength of the negative effects is counteracted by comprehensive explanation and counselling. As previously explained, however, access is not limited to offers of specific countries or of a certified quality. People can purchase genetic DTC tests without integrating a physician, and this may particularly lead to predictive analysis, which has negative consequences for the players on all levels. Therefore, it is the task of the government to develop information structures for the consolidation of public consciousness and consumer sovereignty (information about advantages and disadvantages, chances and risks, quality criteria of analysis, etc.), and expanding infrastructure for human genetic counselling. Further, insurances have the possibility of informing their insured community through awareness campaigns or offers about the chances and risks of genetic analysis, especially regarding genetic DTC tests.

This systematic review has some limitations. In the search strategy, only German terms were used to evaluate the offers, which focus on the German population. However, using English terms for searching genetic analyses may increase the number of hits significantly. However, search terms such as "DNA test" and "DNS test" are the same in German and English. Hence, these lead to an inclusion of webpages, which are providing only information in English. Moreover, this affects only 11% of the included webpages. The internet constitutes a possibility to get access to the global market and, therefore, interested customers may choose from a multitude of offers. This underlines the need of a comprehensive information and education about the risks and concerns of genetic DTC tests. A sole search with language-specific terms leads, despite a highly restricted market, to a plurality of international offers. This may lead to risks or negative consequences for an uninformed citizen who relies on national regulations. Therefore, the population should also be made aware of international offers with possible questionable values and the importance of genetic counselling. Furthermore, using another search engine (e.g., Bing or Yahoo) may lead to other results. However, Google has the highest market share in Germany [80]; thereby, this analysis shows the representative spectrum of offers a German consumer will receive if she or he is searching for genetic tests on the internet. Furthermore, it could be assumed that companies oriented their search engine optimization with Google for a better retrievability. At least, a further limitation could be seen in the potential implications for a solidarily financed health-care system. These implications are speculative as well as not supported by any data. At the time of our study, we did not identify specific economic literature or data for the monetary benefits and/or consequences of genetic DTC testing. However, this discussion may increase the awareness in the different player and policy decision makers of potential cost-increasing consequences as well as lead to further discussions.

Conclusion

The progress in genomics has led to an increased offer of genetic analysis. In Germany, the execution of health-related genetic DTC tests, especially for predictive or diagnostic purposes, is restricted by the GenDG. However, the globalization enables a worldwide access to genetic DTC tests via the internet. Hence, also people in a highly regulated market are confronted with a majority of international offers. This global genetic DTC market is characterized by lack of transparency, and for the individual these various offers are partly or completely not comparable. Primarily, genetic DTC tests are performed on people's own account, but may lead to subsequent costs for a solidarily financed health-care system. Therefore, information and education about chances and risks of genetic DTC tests is a future responsibility of policy decision makers.

Disclosure Statement

The authors declare no conflicting interests.

Author Contributions

Marika Plöthner, the lead author, created the study design and initial draft. Mike Klora, Daniel Rudolph, and Johann-Matthias Graf von der Schulenburg contributed to the manuscript through literature search, discussions on design and structure, writing, and reviews.

References

1 Tulchinsky TH, Varavikova E: The New Public Health, ed 2. Amsterdam/Boston, Elsevier/Academic Press, 2009.
2 Berg S: The well-informed patient: a new breed of health care consumer. Asthma Mag 2005;10:28–30.
3 Diaz JA, Griffith RA, Ng JJ, Reinert SE, Friedmann PD, Moulton AW: Patients' use of the Internet for medical information. J Gen Intern Med 2002;17:180–185.
4 Tonsaker T, Bartlett G, Trpkov C: Health information on the Internet: gold mine or minefield? Can Fam Physician 2014;60:407–408.
5 Hübner M: Dr. Google setzt Ärzte unter Druck. Ärztezeitung online. 2016. http://www.aerztezeitung.de/praxis_wirtschaft/special-arzt-patient/article/913353/umfrage-zeigt-dr-google-setzt-aerzte-druck.html (accessed October 6, 2016).
6 National Institutes of Health: Biological Sciences Curriculum Study. Understanding Human Genetic Variation. 2007. https://www.ncbi.nlm.nih.gov/books/NBK20363/ (accessed December 6, 2016).
7 Hayden EC: Technology: The $1,000 genome. Nature 2014;507:294–295.
8 Manolio TA, Collins FS: The HapMap and genome-wide association studies in diagnosis and therapy. Annu Rev Med 2009;60:443–456.
9 National Human Genome Research Institute: Genome-Wide Association Studies. 2015. https://www.genome.gov/20019523/ (accessed December 6, 2016).
10 Rockman MV: Reverse engineering the genotype-phenotype map with natural genetic variation. Nature 2008;456:738–744.
11 Wray NR, Goddard ME, Visscher PM: Prediction of individual genetic risk to disease from genome-wide association studies. Genome Res 2007;17:1520–1528.
12 O'Daniel JM: The prospect of genome-guided preventive medicine: a need and opportunity for genetic counselors. J Genet Counsel 2010;19:315–327.
13 Mihaescu R, Moonesinghe R, Khoury MJ, Janssens AC: Predictive genetic testing for the identification of high-risk groups: a simulation study on the impact of predictive ability. Genome Med 2011;3:51.
14 Su P: Direct-to-consumer genetic testing: a comprehensive view. Yale J Biol Med 2013;86:359–365.
15 Liu Y, Pearson YE: Direct-to-consumer marketing of predictive medical genetic tests: assessment of current practices and policy recommendations. J Public Policy Market 2008;27:131–148.
16 Global Industry Analysts: Future of Direct-to-Consumer (DTC) Genetic Testing Market Remains Fraught. 2012. http://www.prweb.com/releases/DTC_genetic_testing/direct_to_consumer_tests/prweb9780295.htm (accessed December 6, 2016).
17 US National Library of Medicine: What is direct-to-consumer genetic testing? 2016. https://ghr.nlm.nih.gov/primer/testing/directtoconsumer (accessed December 7, 2016).
18 Lippi G, Favaloro EJ, Plebani M: Direct-to-consumer testing: more risks than opportunities. Int J Clin Pract 2011;65:1221–1229.
19 Kalokairinou L, Howard HC, Borry P: Direct-to-Consumer Genetic Testing. Chichester, John Wiley and Sons, 2001.
20 The German Reference Centre for Ethics in the Life Sciences (DRZE): Predictive Genetic Testing-Medical and scientific aspects. 2011. http://www.drze.de/in-focus/predictive-genetic-testing?set_language = en (accessed December 7, 2016).
21 Gollust SE, Wilfond BS, Hull SC: Direct-to-consumer sales of genetic services on the Internet. Genet Med 2003;5:332–337.
22 Global Industry Analysts: Genetic testing – a global strategic business report. 2015. http://www.strategyr.com/pressMCP-1392.asp (accessed December 12, 2016).
23 XE Currency Converter. Exchange Rates. 2016. http://www.xe.com/ (accessed December 2, 2016).
24 Abnehmgene: Diverse webpage information. 2015. www.abnehmgene.com (accessed November 17, 2016).
25 Adisonlab: Diverse webpage information. 2014. http://www.adisonlab.com/ (accessed November 17, 2016).
26 Amway: Diverse webpage information. 2016. www.amway.de (accessed November 17, 2016).
27 Ceneta: Diverse webpage information. 2016. www.cenata.de (accessed November 17, 2016).
28 Coloalert: Diverse webpage information. 2015. http://www.coloalert.de/ (accessed November 17, 2016).
29 DNAdirekt: Diverse webpage information. 2016. http://www.dna-direkt.de/ (accessed November 17, 2016).
30 DNAfit: Diverse webpage information. 2016. https://www.dnafit.com (accessed November 17, 2016).
31 DNA Plus-Zentrum für Humangenetik: diverse webpage information. 2009. http://www.dnaplus.de/ (accessed November 17, 2016).
32 DTC DNA Testing Center: Diverse webpage information. 2008. http://dnatestingcenter.de/ (accessed November 17, 2016).
33 DNAnutriControl: Diverse webpage information. 2014. http://www.dnanutricontrol.com/ (accessed November 18, 2016).
34 DNA Weight Control: Diverse webpage information. 2014. http://www.dnaweightcontrol.ch/ (accessed November 17, 2016).
35 Dr. Seibt Genomics: Diverse webpage information. 2016. www.dr-seibt-genomics.com (accessed November 17, 2016).
36 EasyDNA: Diverse webpage information. 2016. http://www.easydna.ch/ (accessed November 17, 2016).
37 FutureGenetic: Diverse webpage information. 2016. https://future-genetik.com/ (accessed November 17, 2016).
38 Genetic balance: Diverse webpage information. 2016. https://genetic-balance.com (accessed November 17, 2016).
39 Genoris: Diverse webpage information. 2015. https://genoris.com (accessed November 17, 2016).
40 Geneplanet: Diverse webpage information. 2016. www.geneplanet.de (accessed November 17, 2016).
41 coCap: Diverse webpage information. 2016. www.cogap.de (accessed November 17, 2016).
42 Genovia: Diverse webpage information. 2012. http://genovia-shop.de/ (accessed November 17, 2016).
43 Humatrix: Diverse webpage information. 2016. www.humatrix.de (accessed November 17, 2016).
44 Ilid: Diverse webpage information. 2016. http://www.llid-metacheck.de/ (accessed November 18, 2016).
45 Jenagen: Diverse webpage information. 2016. http://www.jenagen.de/ (accessed November 18, 2016).

46 Lifecodexx: Diverse webpage information. 2015. http://lifecodexx.com/ (accessed November 18, 2016).
47 Lifegenetics: Diverse webpage information. 2016. http://lifegenetics.net/ (accessed November 18, 2016).
48 Meinlabtest: Diverse webpage information. 2016. http://www.meinlabtest.de/ (accessed November 18, 2016).
49 MIADNA: Diverse webpage information. 2016. http://www.miadna.com/ (accessed November 18, 2016).
50 Medical Rogaska: Diverse webpage information. 2015. http://www.rogaska-medical.com/ (accessed November 18, 2016).
51 Nifty: Diverse webpage information. 2014. www.niftytest.com (accessed November 18, 2016).
52 Nutrilite: Diverse webpage information. 2016. https://nutrilitebodykey.de (accessed November 18, 2016).
53 Oncotype: Diverse webpage information. 2016. http://www.oncotypedx.com/ (accessed November 18, 2016).
54 Prenatalis: Diverse webpage information. 2016. www.prenatalis.de (accessed November 18, 2016).
55 Primahome: Diverse webpage information. 2016. https://primahometest.com/ (accessed November 18, 2016).
56 Progenom: Diverse webpage information. 2016. http://www.progenom.com/ (accessed November 18, 2016).
57 SkinDNA: Diverse webpage information. 2015. www.skindna.de (accessed November 18, 2016).
58 Whózthedaddy: Diverse webpage information. 2016. https://www.whozthedad-dy.com (accessed November 18, 2016).
59 Borry P, van Hellemondt RE, Sprumont D, et al: Legislation on direct-to-consumer genetic testing in seven European countries, Eur J Hum Genet 2012;20:715–721.
60 EASAC-FEAM Working Group on Direct-To-Consumer Genetic Testing: Announcement of new project and open Call for Evidence. 2011. http://www.easac.eu/biosciences/current-projects/direct-to-consumer-genetic-testing.html (accessed May 5, 2016).
61 Human Genetics Commission: A Common Framework of Principles for Direct-to-Consumer Genetic Testing Services. 2010. http://www.hgc.gov.uk/Client/document.asp?DocId = 280&CAtegoryId = 10 (accessed May 5, 2016).
62 Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al: Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536:285–291.
63 Business Wire: Research and Markets: Global Health and Wellness Food Market 2015–2019 – Growing Health Awareness among Consumers. 2016. http://www.businesswire.com/news/home/20160111005643/en/Research-Markets-Global-Health-Wellness-Food-Market (accessed December 12, 2016).
64 Gollust SE, Gordon ES, Zayac C, Griffin G, Christman MF, Pyeritz RE, et al: Motivations and perceptions of early adopters of personalized genomics: perspectives from research participants. Public Health Genomics 2012;15:22–30.
65 Anderson AE, Flores KG, Boonyasiriwat W, Gammon A, Kohlmann W, Birmingham WC, et al: Interest and informational preferences regarding genomic testing for modest increases in colorectal cancer risk. Public Health Genomics 2014;17:48–60.
66 Vayena E, Gourna E, Streuli J, Hafen E, Prainsack B: Experiences of early users of direct-to-consumer genomics in Switzerland: an exploratory study. Public health Genomics 2012;15:352–362.
67 Altman RB: Direct-to-consumer genetic testing: failure is not an option. Clin Pharmacol Ther 2009;86:15–17.
68 Roberts JS, Ostergren J: Direct-to-consumer genetic testing and personal genomics services: a review of recent empirical studies. Curr Genet Med Rep 2013;1:182–200.
69 Bloss CS, Schork NJ, Topol EJ: Effect of direct-to-consumer genomewide profiling to assess disease risk. N Engl J Med 2011;364:524–534.
70 Kaufman DJ, Bollinger JM, Dvoskin RL, Scott JA: Risky business: risk perception and the use of medical services among customers of DTC personal genetic testing. J Genet Counsel 2012;21:413–22.
71 Bloss CS, Wineinger NE, Darst BF, Schork NJ, Topol EJ: Impact of direct-to-consumer genomic testing at long term follow-up. J Med Genet 2013;50:393–400.
72 National Human Genome Research Institute: Genetic Discrimination. 2016._https://www.genome.gov/10002077/genetic-discrimination/ (accessed December 7, 2016).
73 Patenaude AF: Addressing Psychological Impacts of Genetic Testing on Patients, Families. Washington, American Psychological Association, 2013. http://www.apa.org/news/press/releases/2013/05/genetic-testing.aspx (accessed December 7, 2016).
74 O'Neill SC, Tercyak KP, Baytop C, Hensley Alford S, McBride CM: A new approach to assessing affect and the emotional implications of personal genomic testing for common disease risk. Public Health Genomics 2015;18:104–112.
75 Hilgart JS, Coles B, Iredale R: Cancer genetic risk assessment for individuals at risk of familial breast cancer. Cochrane Database Syst Rev 2012;CD003721.
76 Hubbard R: Predictive genetics and the construction of the healthy ill. Suffolk Univ Law Rev 1993;27:1209–1224.
77 Jamison DT: Disease Control Priorities in Developing Countries, ed 2. New York, Washington, Oxford University Press, 2006.
78 McPherson E: Genetic diagnosis and testing in clinical practice. Clin Med Res 2006;4:123–129.
79 Ostergren JE, Gornick MC, Carere DA, Kalia SS, Uhlmann WR, Ruffin MT, et al: How well do customers of direct-to-consumer personal genomic testing services comprehend genetic test results? Findings from the Impact of Personal Genomics Study. Public Health Genomics 2015;18:216–224.
80 Statista: Market share of leading search engines in Germany between 2014 and 2016. 2017. https://de.statista.com/statistik/daten/studie/167841/umfrage/marktanteile-ausgewaehlter-suchmaschinen-in-deutschland/ (accessed May 2, 2017).