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Übernahme von im Ausland durchgeführten Laboranalysen zu Lasten der obligatorischen Krankenpflegeversicherung (OKP)

Sehr geehrte Damen und Herren

Im Zusammenhang mit BRCA1- und BRCA2-Untersuchungen erlauben wir uns folgende Bemerkungen:

1. Rechtliche Grundlagen

Zwischen der Schweiz und der Europäischen Union besteht derzeit (noch) kein vertragliches Dienstleistungsfreizügigkeitsabkommen. Entsprechend ist in der schweizerischen Krankenversicherung grundsätzlich das Territorialitätsprinzip massgebend, d. h., es werden grundsätzlich nur jene Leistungen übernommen, die in der Schweiz erbracht werden. Die Krankenversicherungsgesetzgebung und das EU-Koordinationsrecht im Bereich der sozialen Sicherheit sehen jedoch gewisse Ausnahmefälle vor, in denen die obligatorische Krankenpflegeversicherung (OKP) die Kosten von Leistungen übernimmt, die im Ausland erbracht werden. [1]

Es sind dies:

- Die notwendigen medizinischen Behandlungen während eines vorübergehenden Auslandaufenthaltes (Artikel 36 der Verordnung über die Krankenversicherung [KVV] / Artikel 19 VO (EG) 883/2004, Titel III, Kapitel 1, Abschnitt 1)
- Die Behandlungen im Ausland aus medizinischen Gründen, nach vorgängigem Einverständnis des zuständigen Krankenversicherers (Artikel 36 KVV)
- Die im Koordinationsrecht der EU vorgesehenen Zustimmungsfälle (Artikel 20 VO (EG)

[1] vgl. in diesem Zusammenhang das Informationsschreiben des BAG vom 8. April 2008 über die medizinische Behandlung im Ausland, abrufbar unter:
http://www.bag.admin.ch/themen/krankenversicherung/00316/03846/index.html?lang=de

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883/2004, Titel III, Kapitel 1, Abschnitt 1)

Die Durchführung von Laboranalysen im Ausland aus Untersuchungsproben aus der Schweiz fällt jedoch unter keine dieser vorstehend erwähnten Ausnahmefälle. In der Analysenliste, die eine sog. Positivliste darstellt, sind sämtliche zu Lasten der OKP durchführbaren Analysen abschliessend aufgeführt. Falls eine dieser Analysen im Ausland zu Lasten der OKP durchgeführt werden kann, so ist diese Analyse mit dem entsprechenden Vermerk über die Durchführung im Ausland versehen. Ist dies nicht der Fall, stellt eine im Ausland durchgeführte Laboranalyse keine Pflichtleistung der OKP dar. Wir verweisen in diesem Zusammenhang auf unser früheres Rundschreiben vom 19. Dezember 2003[2], das weiterhin Gültigkeit hat. Ohne das Territorialitätsprinzip wären u.a. die schweizerischen Zulassungsbedingungen und die Qualitätssicherungsvorschriften für Laboratorien nicht durchzusetzen. Gemäss der Verordnung über genetische Untersuchungen beim Menschen (GUMV) ist es zwar erlaubt, molekulargenetische Untersuchungen im Ausland unter Gewährleistung des Stands von Wissenschaft und Technik durchführen zu lassen. In Bezug auf die Verrechnung zu Lasten der OKP ist jedoch einzig das Krankenversicherungsgesetz (KVG) massgebend. Zur Zeit sind einzig die sog. Orphan Disease-Positionen im Kapitel Genetik der Analysenliste mit dem Vermerk über die Durchführung im Ausland versehen.

2. Qualitätsaspekte betreffend Aussagekraft der Ergebnisse und zeitliche Verfügbarkeit der Resultate

BRCA1- und BRCA2-Untersuchungen (Positionen 2125.01, 2225.01, 2325.01, 2425.01 und 2525.01, der Analysenliste) werden in der Schweiz durch Laboratorien, die nach dem Bundesgesetz über genetische Untersuchungen beim Menschen (GUMG) über eine Bewilligung verfügen, durchgeführt und können zu Lasten der OKP abgerechnet werden. Betreffend Aussagekraft der BRCA-1 und BRCA-2 Analysen sind unserem Amt keine Anhaltspunkte bekannt, wonach Qualitätsunterschiede zu ausländischen Laboratorien oder Unternehmen, insbesondere zu Myriad Genetics, bestehen. Myriad Genetics macht zwar gegenüber europäischen Ländern eine viel kleinere Rate von Untersuchungsresultaten mit unklarer Bedeutung (Variants of Uncertain Significance, VUS) geltend. Dies wird aber nicht durch Studien objektiv belegt. Zum Vergleich von VUS-Raten wäre die Bekanntgabe des Algorithmus für die Klassierung der BRCA1- und BRCA2-Mutationen und die Definition von VUS notwendig. So existieren je nach Datenbank verschiedene Algorithmen für die Klassierung der BRCA1- und BRCA2-Mutationen. Myriad Genetics speist ihre Ergebnisse nicht in die bestehenden öffentlichen Datenbanken ein, sondern führt die Auswertung der BRCA1- und BRCA2-Mutationen gestützt auf ihre eigene Datenbank durch, die nicht öffentlich zugänglich ist.

Wir verweisen in diesem Zusammenhang gerne auf den kürzlich erschienen Artikel von Cook-Deegan et al. im European Journal of Human Genetics „The next controversy in genetic testing: clinical data as trade secrets?" (vgl. Beilage). Danach hängt die Interpretation der klinischen Bedeutung von festgestellten genetischen Laborbefunden vom öffentlichen Zugang zu den genauen Untersuchungsresultaten und der klinischen Information über die getesteten Personen ab. Es wird von den Autoren weiter erläutert, Myriad Genetics mache eine VUS-Rate von 3 % gegenüber 20 % in europäischen Ländern geltend. Diese Diskrepanz hänge mindestens teilweise mit dem alleinigen Besitz der Information zusammen, die für die Interpretation von VUS-Resultaten nötig sei. Seit 2004 habe Myriad Genetics keine eigenen Daten mehr veröffentlicht bzw. in die öffentlichen Datenbanken eingespeist. Danach habe Myriad Genetics zwar die grösste existierende Studie über die Auswertung von VUS-Resultaten durchgeführt und publiziert, jedoch die DNA-Sequenzen der VUS-Resultate nicht aufgelistet und die genauen Algorithmen für die Interpretation der VUS-Resultate nicht mitgeteilt, so dass Dritte diese Auswertung der Daten nicht nachvollziehen könnten. Weiter wird ausgeführt, die Kostenträger in den USA hätten die Probleme im Zusammenhang mit dem unvollständigen Zugang zu medizinischen Daten nicht vorhergesehen und keine Massnahmen zur Sicherstellung der unabhängigen Bestätigung

[2] abrufbar unter:
http://www.bag.admin.ch/themen/krankenversicherung/00263/00264/04185/06672/index.html?lang=de

der Prognosen getroffen, die aufgrund der Laborresultate an die Patienten abgegeben wurden. Mit dem Eintritt von Myriad Genetics in den Europamarkt 2012 hätten die zuständigen Entscheidungsträger die Möglichkeit, sicherzustellen, dass die Daten, welche für die Interpretation der klinischen Bedeutung von genetischen Laborbefunden nötig sind, öffentlich gemacht werden. Damit könnten die Daten einer genauen Überprüfung unterzogen werden und wären zum Vorteil von Patienten und medizinischen Berufspersonen zugänglich.

Gemäss Information der schweizerischen Laboratorien, die BRCA1 und BRCA2 analysieren, beträgt deren VUS-Rate zwischen 4 % und 7 %. Somit differieren die VUS-Raten zwischen Myriad Genetics und den schweizerischen Laboratorien zur Zeit um höchstens einige wenige Prozentpunkte, was für sich alleine gesehen keinen Qualitätsunterschied ausmacht. In sämtlichen europäischen Laboratorien sind in den letzten Jahren die VUS-Raten dank der Wissenszunahme aufgrund der öffentlichen Datenbanken gesunken. Auch ist die zeitliche Verfügbarkeit der schweizerischen Untersuchungsergebnisse genügend sichergestellt. Der Median- und Mittelwert für die Bearbeitungszeit beträgt gemäss den neusten Informationen der schweizerischen Laboratorien für das Jahr 2013 lediglich noch 19 Tage.

Die Untersuchung der Gene BRCA1 und BRCA2 stellt im übrigen kaum eine Notfalldiagnostik dar. Die Diagnose von Brustkrebs wird nach wie vor mit der zytologisch/histologischen Untersuchung einer Tumorprobe vorgenommen. Die Untersuchung der Gene BRCA1 und BRCA2 aus einer Blutprobe dient dem Nachweis einer Veranlagung für das erbliche Brust- oder Ovarialkrebs-Syndrom. Falls diese Veranlagung bei einer an Krebs erkrankten Patientin gefunden wird, so handelt es sich bei dieser Patientin um eine erbliche Form von Brustkrebs. Wird diese Veranlagung bei gesunden Familienangehörigen der erkrankten Patientin festgestellt, so kann eine Prognose für das Risiko, im Laufe des Lebens an Krebs zu erkranken, gemacht werden.

Nur eine Minderheit der neu diagnostizierten Brust- oder Ovarialkrebserkrankungen ist erblich bedingt, weswegen auch nur bei bestimmten, gewisse Kriterien erfüllenden Patientinnen und deren Angehörigen eine Untersuchung auf BRCA1 und BRCA2 angezeigt ist. In der Schweiz ist zum Zeitpunkt der Erstbehandlung des Krebses schätzungsweise bei weniger als 2 % der Patientinnen eine BRCA1- und BRCA2-Untersuchung durchgeführt worden. Vom medizinischen Standpunkt aus besteht keine Notwendigkeit, bei einer Patientin mit erstmals diagnostiziertem Brustkrebs bereits zum Zeitpunkt der Erstbehandlung des Krebses die Resultate der BRCA1- und BRCA2-Untersuchung zu kennen.

3. Tarifierung

Was die Tarife betrifft, so hat das BAG seit längerer Zeit Schritte im Hinblick auf eine Tarifsenkung von BRCA1 und BRCA2 in der Analysenliste eingeleitet und zu diesem Zwecke auch Kontakt mit den Laboratorien des Kantonsspitals Aarau und des Universitätsspitals Genf aufgenommen. Die beiden Spitäler verlangen - gestützt auf einen Hinweis des BAG, dass der Tarif der Analysenliste einen Höchsttarif darstellt und es den Leistungserbringern unbenommen ist, einen tieferen Tarif in Rechnung zu stellen - für die vollständige Untersuchung von BRCA1 und BRCA2 pauschal nur noch CHF 4300.--.

Besten Dank für Ihre Kenntnisnahme und die Einhaltung der gesetzlichen Grundlagen.

Freundliche Grüsse

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The next controversy in genetic testing: clinical data as trade secrets?

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Sole-source business models for genetic testing can create private databases containing information vital to interpreting the clinical significance of human genetic variations. But incomplete access to those databases threatens to impede the clinical interpretation of genomic medicine. National health systems and insurers, regulators, researchers, providers and patients all have a strong interest in ensuring broad access to information about the clinical significance of variants discovered through genetic testing. They can create incentives for sharing data and interpretive algorithms in several ways, including: promoting voluntary sharing; requiring laboratories to share as a condition of payment for or regulatory approval of laboratory services; establishing – and compelling participation in – resources that capture the information needed to interpret the data independent of company policies; and paying for sharing and interpretation in addition to paying for the test itself. US policies have failed to address the data-sharing issue. The entry of new and established firms into the European genetic testing market presents an opportunity to correct this failure.
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BACKGROUND

Interpreting the clinical significance of genomic information depends on broad access to DNA sequence variants and clinical information about those tested. Some proprietary genetic test providers have developed privately controlled databases containing information essential to interpreting the results of their tests. This is exemplified by *BRCA1/2* testing by Myriad Genetics (Salt Lake City, UT, USA) in the United States.

As the provider of BRACAnalysis, the sole *BRCA1/2* diagnostic test commercially available in the United States and one of the most commercially successful genetic tests worldwide, Myriad Genetics serves as an excellent case study of the importance of collecting clinical data and the implications of keeping those data private. Myriad Genetics has enjoyed market success with BRACAnalysis – Myriad notes that nearly one million patients have had BRCA testing, and it has payment agreements with 2500 insurers or payers.[1] Its status as the sole commercial provider of BRCA testing in the United States is a consequence of its exclusive US patent rights. In 1994, scientists, some of whom were affiliated with Myriad, discovered *BRCA1*, which when mutated results in pronounced predisposition to breast, ovarian and certain other cancers.[2–4] Myriad-associated scientists co-discovered the *BRCA2* gene the following year. Myriad patented its discoveries and acquired *BRCA* patent rights from others. It became the sole commercial testing service for *BRCA1/2* in the United States by asserting its patents and clearing the market of US competitors,[5] generating over $105 million from its BRACAnalysis test in the second quarter for calendar year 2012.[6]

Myriad has several competitive advantages based on its long experience in *BRCA* testing. It runs a highly efficient laboratory, has developed a network of health professionals who use its services, has secured agreements with hundreds of payers, has brand recognition based in part on direct-to-consumer advertising, and has a trained sales force. Although those advantages should abide any change in patent status or data access policies, Myriad's entry into Europe, projected for later this year,[6] presents an opportunity to implement policies on access to *BRCA* mutation data that can set a salutary precedent not only for *BRCA* but for genetic testing in general, including whole-genome analysis.[7,8]

INTERPRETING VARIANTS OF UNKNOWN SIGNIFICANCE

Most patients who get *BRCA* testing have results that can be interpreted in a relatively straightforward manner – either no variations from 'wild type', harmless sequence variations or a clearly deleterious mutation. Such results are valuable to those tested and to their providers, influencing decisions about treatment options, including prophylactic surgery or close monitoring and medical management. Mutations that clearly disrupt protein function (e.g., through a small insertion or deletion that results in a frame shift) are generally obvious upon inspection.

In a significant minority of tests, however, sequence differences from wild type are difficult to interpret. These are 'variants of unknown significance' (VUS). Missense mutations that substitute one amino acid for another or changes near intron–exon boundaries can be particularly difficult to interpret. Myriad claims that the fraction of cases resulting in a VUS is 3% in its hands, and 20% for most European *BRCA*-testing services.[1] This discrepancy is at least in part due to Myriad having sole possession of the information needed to interpret VUS results. Myriad has obtained this exclusivity by using its status as the sole *BRCA1/2* test provider to develop, at its own cost, an extensive database that relates variants of uncertain significance to phenotype, details their frequency in various populations and includes genetic studies on patient families. Thus, Myriad's proprietary database that contains information about variants, which is not found in public databases, is probably the major

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factor in explaining the company's ability to interpret VUS results more successfully than others.

To its credit and the benefit of patients, Myriad has used its database to reduce the frequency with which it reports a VUS. When Myriad finds a new VUS – or one previously identified but whose clinical significance is not yet understood – it offers free testing to the patient's family members (something that not all genetic testing laboratories do) in an effort to help determine the variant's significance. Myriad encourages the person with the VUS to contact others in their family, providing a model letter that patients can send their relatives. Myriad collects data regarding the clinical outcome associated with that VUS, and a VUS may ultimately be reclassified as deleterious or neutral as more is learned; conversely, deleterious or neutral mutations are occasionally reclassified as VUSs.

Myriad has access to public databases in interpreting mutations, but outsiders do not have access to Myriad's database. This asymmetry has clinical impact: a woman might be able to receive *BRCA* testing from another laboratory in Malawi or Malta, where Myriad's *BRCA* patent rights are not in force and testing is perfectly legal, but that laboratory will have no access to Myriad's data and will thus be unable to interpret many VUS results. Geographic inequities are common in the market for medical products and services. But the fact that the inequity is based on the availability of basic scientific and medical information, rather than of a drug or product, changes the policy context, prompting a debate about keeping clinically relevant data proprietary when that secrecy makes independent verification of its medical significance impossible.

In an environment in which new technologies, including whole-genome and whole-exome sequencing, are already beginning to change clinical practices in genetic testing,[9–11] a proprietary database gives Myriad indefinite exclusivity independent of patent protection. Even if Myriad's patents are invalidated (for a summary of the ongoing court challenge, see Supplementary materials), or new alternative testing technologies do not infringe them, until the data and interpretive algorithms are re-created in publicly accessible form, competing services will be able to manage VUS results in only two ways: by having samples analyzed at Myriad, where it is interpreted in light of Myriad's proprietary database, or by rendering inadequate interpretations based upon incomplete public data and algorithms. The former perpetuates Myriad's exclusivity even after the expiration of its patent rights, while the latter is unacceptable from a clinical perspective. In either case, current practice permits the privatization of valuable clinical data obtained from patients.

DATA-SHARING PRACTICES

Myriad contributed data to public databases until late 2004, but since then its contributions have essentially stopped. Its last major deposit of data to the Breast Cancer Information Core (BIC, the largest database for BRCA mutations, maintained by the National Human Genome Research Institute) was in November 2004. Myriad officials explained to one of us (RC-D) that the decision not to share data was initially because of difficulties in matching data formats, but that after 2005, the company adopted a deliberate policy of retaining data as a trade secret.

Myriad has published some articles on VUS data since November 2004 when its public data-sharing stopped. Investigators with access to the Myriad database through 2006, did the most extensive analysis of VUS, reporting 18 deleterious and 100 neutral variants out of 1433 variants they studied.[9] Those 118 sequence variants of known significance are now in the public literature. More than 1200 variants are mentioned in that publication, but the sequences are not listed, and the interpretive algorithms are not specified in detail or deposited where others can use them to interpret the data. Thus, Myriad's general approach to 'calling' VUS results is described, but neither analytic algorithms nor underlying sequence data are available.[9–13] This contrasts with recommendations of the National Academies in two reports that call for depositing data and methods sufficient for replication and interpretation.[14,15]

Myriad's exclusive US testing rights and its pursuit of cases of VUS have enabled it to accumulate data that confer a proprietary advantage in *BRCA* test interpretation worldwide. Some will surely point to this as a legitimate benefit bestowed by the patent system, part of Myriad's just reward for innovating. Patents gave Myriad exclusive access to those seeking genetic testing, which enabled Myriad, in turn, to produce a valuable database. Others, however, are likely to consider the withholding of unpatented patient data to hinder rather than 'to promote the progress of science and useful arts,' the Constitutional mandate upon which the US patent system is founded. Arguments that focus on rewarding innovation, moreover, must also take into account that much of the work that led to the isolation of *BRCA1/2* was done with public or nonprofit funding. The practical effect of retaining such data as a trade secret is to extend Myriad's testing monopoly beyond the life of the patents on which it was founded.

Whole genome analysis stands poised to have a major impact on medical care if it can be harnessed appropriately. But the biggest challenge to its implementation is properly interpreting the variants found upon analyzing any individual's genome. As whole-genome and whole-exome sequencing become commonplace, the rate of truly novel mutations will eventually decline. For the foreseeable future, however, each individual whose genome is sequenced will have vast numbers of variants of uncertain clinical significance.

Comprehensive databases such as The Human Gene Mutation Database in Cardiff, MutaDATABASE, the Human Variome Project database, the Leiden Open Variation Database, and other public databases will be essential resources for tracking and interpreting VUS data. Those databases depend, however, on sharing sufficient information to make genotype–phenotype correlations. Myriad, Prevention Genetics and Medical Neurogenetics are the only three laboratories not agreeing to contribute data on human genetic variants to MutaDATABASE, in contrast to over 100 services that have agreed to contribute mutation data (including GeneDx, Quest/Athena, LabCorp and other large commercial testing services).[16] The Evidence-based Network for the Interpretation of Mutant Germline Alleles (ENIGMA) was funded as a US National Institutes of Health challenge grant in 2009 to focus on interpreting VUS results from *BRCA* genes in the public domain.[17–19] It draws from databases and colleagues around the world to apply bioinformatic and laboratory biological methods to improve VUS interpretation. ENIGMA has access to data in Myriad's database through 2006, but not from the past 5 years.

The objective of these databases and research consortia is to accumulate data and to refine interpretive methods to create a publicly available foundation for improving clinical interpretation of genetic testing. As these public resources accumulate data, the value of proprietary databases will eventually erode, but in the meantime clinicians will be ordering and health plans will be paying for many genetic results that cannot be accurately interpreted based on publicly available information.

POLICY OPTIONS

To deal with this conundrum, one set of policy options involves leveraging the influence of scientific journals and organizations by

applying existing disclosure standards. Medical journals and scholars have legitimate claims on data and methods for clinical interpretation of mutations. The 2003 National Academies report on publication of genomic data recommended that 'authors should include in their publications the data, algorithms or other information that is central or integral to the publication – that is, whatever is necessary to support the major claims of the paper and would enable one skilled in the art to verify or replicate the claims'.[15] The Uniform Requirements for Submission of Manuscripts to Medical Journals mandates that authors 'identify the methods... and procedures in sufficient detail to allow others to reproduce the results'.[20] The importance of replicability and objective, independent access to data and algorithms was reiterated in the March 2012 report from the Institute of Medicine (IOM), which recommended that 'data and metadata used for development of the candidate omics-based test should be made available in an independently managed database'.[14] IOM also recommended that computer code and computational methods be fully shared, either through a public database, publication or in the process of regulatory review. These criteria imply a norm of access to data and analytical methods sufficient to make clinical inferences about VUS results.

Leveraging publication standards holds promise but also has limitations. Some journals already require public deposit of data sufficient to independently interpret reported mutations. But as noted above, Myriad's publications gave the sequences of only 118 of more than 1400 mutations studied, and did not include the interpretive algorithms. Publication guidelines, moreover, apply only when the benefits of publication are sought; they obviously do not apply to unpublished VUS data.

As a related option, databases listing mutations or availability of genetic tests (e.g., the NIH's nascent Genetic Testing Registry) could mandate test providers share sequence data and interpretive algorithms as a condition of listing their tests. In addition, physicians receiving results, or the organizations that collectively represent them, could also demand access to underlying data and algorithms. For example, standards for reporting such results could be established by the European Society for Human Genetics or international scientific and medical organizations.

Another set of options would rely on the power of payers and regulators. Payers currently reimburse bundled genetic tests and interpretive services. In cases when interpretation cannot be independently verified, payers would be on firm ground to request – or demand – the evidence underlying the clinical determinations.

National health systems, insurers and regulators have several policy tools at their disposal to ensure independent validation of clinical inferences about genomic variants. First, they could ask testing firms to voluntarily adopt policies to share mutation data publicly. Second, payers could refuse payment unless clinically relevant data are shared and subject to independent verification for both accuracy and validity of interpretation. This option further bifurcates into (1) disclosure only to payers or providers, or (2) full public disclosure. That is, if payers mandated data access, disclosure could be limited to regulatory authorities or to those making coverage and payment decisions. Alternatively, payers could require – as a condition of payment – deposit of data and interpretive algorithms into public databases to enable open and independent evaluation, building on the IOM recommendations. Similarly, national authorities that regulate genomic tests could mandate public disclosure as a condition of pre-market approval. Third, national and international institutions could fund research to re-create the data in proprietary databases by ensuring that results of genetic analysis get incorporated into large databases. Such an option, although redundant and thus expensive, might be accomplished through electronic health records that include genomic as well as clinical data, or by building out from consortia such as ENIGMA that have been established for just this purpose – to collect data and develop analytical methods as a public research and clinical resource. Fourth, national health systems could craft payment policies to create incentives for disclosure of data needed to interpret genetic tests – for example, establishing payment codes for public deposit and interpretation of genomic data, in addition to performing the test itself – thus rewarding firms that disclose valuable data.

CONCLUSION

Current practices of proprietary databases may hinder interpretation of genomic data and impede the advance of personalized medicine. Policies to reward or require data sharing can prevent some foreseeable problems caused by limited access to proprietary data about the clinical significance of genetic variations. Myriad Genetics, for example, has leveraged its *BRCA* patents to become the dominant *BRCA* testing service and, in turn, to create a valuable database. Myriad clearly sees its proprietary database as a source of competitive advantage, one that will persist after its underlying patents expire or are invalidated in court. Because of its public profile and explicit, data-based business plan, Myriad's entry into Europe will force policy choices into stark relief, just as the reduced cost of full-genome analysis brings a worldwide deluge of genomic data. Payers in the United States did not foresee the problems of incomplete access to data, and did not put in place policies to ensure independent verification of clinical predictions. Hundreds of agreements have been signed between genetic testing firms and US payers that have apparently not required disclosure of the underlying data, which is ultimately derived from – and would benefit – patients seeking optimal treatment. Payers and regulators in Europe, South America, Asia and other markets need not be so passive. With the entry of Myriad into Europe in 2012, those making policy decisions about regulation, coverage and reimbursement of genetic tests in Europe can ensure that the data necessary to interpret the clinical significance of genetic variations are made public, where they can be subjected to scientific scrutiny and be available to benefit patients and health professionals around the world.

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