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to collect the data necessary to be certain that appropriate use of antibiotics is included in these programs. It should not be ignored that pharmaceutical companies need to ensure that antibiotic drugs are ethically promoted. Lastly, effective hygiene and infection prevention measures can reduce the incidence of infections^{3,4}.

If the world health community is to effectively deal with the threat of AMR, then the above proposals should be systematically and seriously addressed. That means that there must be the concurrent political will to implement them. In the absence of effective measures being taken, it has been estimated that a continued rise in resistance would lead by 2050 to 10 million people dying every year and would cost the world up to \$100 trillion³. Collaboration and commitment

are essential. Increased funding will help but will not be enough.

COMPETING FINANCIAL INTERESTS

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genes, thus invalidating five patents held by Myriad Genetics (Salt Lake City, UT, USA) and clearing the way for other laboratories to offer tests with the *BRCA1/2* genes². Before June 2013, Myriad was the sole provider of *BRCA1/2*-only tests for clinical use, other than tests limited to single-site analysis, and there were no commercially available *BRCA1/2* panels. The analysis of the *BRCA1/2* testing landscape presented here is the first since the historic 2013 Supreme Court decision that allowed the entry of new testing providers. We identified commercially available and soon-to-be-available *BRCA1/2*-only tests and panels and collected data about the price and scope of testing for each. Because access to genetic tests is considerably influenced by insurance coverage^{3,4}, we also reviewed publicly available coverage policies from private payers. Although past studies have demonstrated that most payers cover *BRCA1/2* testing in indicated populations in accordance with National Comprehensive Cancer Network guidelines^{5–7}, coverage policies have not been examined since the launch of new *BRCA1/2*-only tests and panels to assess whether and how policies have changed.

We identified laboratories offering *BRCA1/2* tests and panels through test registries and gray literature (the US National Institutes of Health Genetic Testing Registry, <http://www.ncbi.nlm.nih.gov/gtr/>; Genetests.org, <http://genetests.org>; the Association for Molecular Pathology Test Directory, <http://www.amptestdirectory.org/index.cfm>;

Availability and payer coverage of *BRCA1/2* tests and gene panels

To the Editor:

In recent years, genetic testing for heritable cancer syndromes has been shifting from single-gene analysis to multigene panels, typically using next-generation sequencing (NGS) technologies. As a correspondence in your October issue¹ described, despite the increasing use of NGS in clinical practice, regulatory standards remain vague and payers have not adopted clear coding and reimbursement guidelines¹. To help clarify the impact of these issues on the availability of testing, we review pricing and payer coverage of *BRCA1/2* tests (providing determination of the entire nucleotide sequence for the *BRCA1* and *BRCA2* genes) and panels containing *BRCA1/2* ('panels'). We find that the number of *BRCA1/2*-only tests and panels has increased since June 2013, and average price has decreased. Even so, many payers consider panels investigational or experimental, although they have positive coverage policies for *BRCA1/2* testing. Although 76% of payers have coverage policies about panels, none of these policies provides positive coverage. Of payers with policies on panels, most (77%) consider panels investigational or experimental, and the remainder limits coverage to those panels on which all the genes are considered medically necessary. The experience with *BRCA1/2* may be instructive in understanding the evolution

of testing and payer coverage toward multigene panels in other indications as well, particularly those with a substantial patient population eligible for testing.

For *BRCA1/2* testing, the shift toward gene panels has primarily occurred because the US Supreme Court ruled in June 2013 that companies may not patent isolated

Figure 1 Pricing for *BRCA1/2*-only and panel tests. Error bars represent the minimum and maximum values, the boxes show the 25th percentile to 75th percentile and the middle horizontal line shows median value. Two-gene test prices ranged from \$500 to \$2,895, with a mean price of \$1,711 versus \$4,040 for Myriad's standard offering, Integrated BRACAnalysis. Pricing for panels including the *BRCA1/2* genes ranged from \$1,500 to \$6,749 with a mean price of \$3,357. Illumina's TruGenome Predisposition Screen (*BRCA* gene analysis in a panel of 1,600 genes, \$9,500) was excluded as an outlier.

Table 1 Payer^a coverage policies for gene panels including *BRCA1/2*

Aspect of payer coverage	Percentage of policies satisfying criteria (number/total relevant policies)
Payers with any relevant coverage policies	76 (13/17)
Panels considered medically necessary and covered	0 (0/13)
Panels covered only if all individual components are medically necessary	23 (3/13)
All panels considered investigational/experimental	54 (7/13)
Specific panels considered investigational/experimental	23 (3/14)
Payers with no relevant coverage policies	24 (4/17)

^aPayers include United Healthcare, Anthem, Aetna, Health Care Service Corporation (HCSC), Cigna, Humana, Health Net, Highmark, Independence Blue Cross, Blue Cross Blue Shield (BCBS) Michigan, CareFirst BCBS, BCBS Tennessee, BCBS Alabama, Blue Shield of California, BCBS Florida, Medical Mutual of Ohio and BCBS Massachusetts. These payers combined represent 158,974,237 covered lives.

NextGx Dx's (Franklin, TN, USA) Genetic Testing Resource, <https://www.nextgdx.com/>; and publisher GenomeWeb (New York), <https://www.genomeweb.com/>) and reviewed laboratory websites to code tests offered, list price and genes included (**Supplementary Methods**). There are 20 *BRCA1/2*-only tests and 36 panels now available or pending launch (as of 7/2014: **Supplementary Table 1**). The average price of *BRCA1/2* testing has dropped, with all new *BRCA1/2*-only tests priced significantly below Myriad's tests (mean price for new *BRCA1/2*-only tests is \$1,711 versus \$4,040 for Integrated BRACAnalysis, Myriad's standard option, $P < 0.01$; **Fig. 1**). Panels are more expensive than new *BRCA1/2*-only tests on average (mean price \$3,357), but 70% are less expensive than Integrated BRACAnalysis (**Fig. 1**). We were unable to access contract pricing or rebating between individual diagnostic providers and payers and therefore cannot comment on the actual cost of each test to payers. However, list prices are indicative of the overall trends in the marketplace.

To evaluate payer coverage of panels, we reviewed publicly available coverage policies from the largest private payers and coded coverage determinations and criteria used (as of May 2015; **Supplementary Tables 2 and 3**). Although payers with policies about *BRCA1/2* testing universally cover two-gene testing in high-risk populations, none of the 17 payers reviewed explicitly covered panels that include *BRCA1/2* (**Table 1**), and the majority considered all panels investigational or experimental. Three payers noted that panels may be considered medically necessary only if testing of all included genes are considered medically necessary, effectively excluding all currently available panels. Among payers who offer rationales for their policies on panels, most cite the lack

of clinical utility and/or clinical validity (data not shown).

Concerns about reimbursement issues may lead some physicians to avoid tests for which such issues are most common³. Because of the lack of coverage for panels, some laboratories may run full panels and bill payers only for the covered *BRCA1* and *BRCA2* genes; Washington University in St. Louis has had success obtaining reimbursement for their tumor panel using a similar approach⁸. However, one payer in our sample (Humana (Louisville, KY, USA); **Supplementary Tables 2 and 3**) specifically ruled out that option for *BRCA1/2* testing. Additionally, if laboratories bill with the same method for *BRCA1/2* testing and for panels, panels may not be covered for patients who have already had *BRCA1/2* testing.

Understanding coverage policies is important, even though some panels are currently reimbursed despite the lack of positive coverage policies. We have found that payers are increasingly concerned about their inability to enforce their coverage policies and are thus implementing internal claims reviews and analytics to identify panels and deny related claims⁹. In the future, as the American Medical Association (Chicago) develops specific current procedural terminology codes for genetic panels, payers will be better able to enforce their coverage policies.

Thus, the increase in availability of panels allows physicians and patients to get more information for comparable prices, but it is not yet clear how and when panels should be used. Specific panels recently have been shown to identify more clinically actionable mutations than testing for *BRCA1/2* tests alone, providing support for the clinical relevance of panel testing^{10–12}. Even so, the clinical validity and clinical utility of many included genes require further research, and the optimal number and identity of genes to test have not

been defined¹³. In addition to questions about clinical utility and payer coverage, panels also raise questions about how to interpret the results given that they return variants of unknown significance and also incidental findings^{10,12–15}.

Furthermore, the services offered by each laboratory may differ, as well as the NGS technologies used to conduct the test. Oversight of NGS technologies, which are used for virtually all of the new tests, contains many gaps¹. Our analysis did not include an evaluation of the analytic validity of new tests, and only limited studies exist on how newer laboratories compare to Myriad's tests in that regard¹². The supplementary services offered (follow-up as new results and variant classifications become available, assistance with reimbursement, patient education materials) may also differ between laboratories.

In conclusion, we found that *BRCA1/2* test options have increased and prices have decreased. Nearly all payers have positive coverage policies for *BRCA1/2*-only testing, but despite the increasing availability of panels, private insurers do not currently formally cover these panels. In their coverage documents, payers cited limited data regarding clinical validity and clinical utility as justification for not covering panels, and routine use of panels has not yet been recommended in guidelines⁵. The comparative effectiveness and cost effectiveness of panels versus single-gene tests have also not been established. Future research on these issues will help define the appropriate use of panels and likely lead to changes in payer coverage policies regarding panels. These issues will accelerate in importance as test panels for other genes and conditions enter clinical care.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.3322).

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The payers' perspective on gene therapies

To the Editor:

In last September's issue, Troyen Brennan and Jim Wilson made the case for a pay-for-performance model for gene therapies¹. The Western world's first gene therapy, Glybera (alipogene tiparvovec), is launching in Germany at an initial €1.1- (\$1.22)-million price tag, a new record for a medicine to treat a rare disease². Several other gene therapies are in late-stage development, and both large pharmaceutical and biotech companies have been building their internal capabilities and striking multiple partnerships³. The financial community has also shown great appetite driven by the promise of high drug prices and recurring payments. However, 'payers,' either public or private, are concerned with both the price levels routinely mentioned for gene therapies and the pricing and reimbursement (P&R) approaches being proposed. Here we report payer attitudes to P&R for gene therapy. We detail why the payers' view differs from that of industry executives, financial analysts and academic experts. And finally, we provide alternative approaches developed through discussions with payers in the United States and large European countries.

Many stakeholders claim that gene therapies require new P&R approaches to achieve a fair recognition of value for developers while providing broad access to

patients and an acceptable budget impact on health systems¹. The current conventional wisdom builds upon two premises. First, gene therapies provide long-term or definitive benefits. Therefore, pricing them as multiples of the yearly cost of expensive drugs such as protein replacement therapies is justified. This leads to prices in excess of \$1 million or \$1.5 million per treatment. And second, a new reimbursement system is required to absorb such high prices. The most likely approach is a capped annuity with risk sharing, allowing health systems to spread the cost over several years and to limit risk if efficacy is not maintained¹.

Unfortunately, these premises are strongly questioned by the people who ultimately carry the financial burden of gene therapies: payers. Those who reimburse treatments are skeptical for two main reasons. First, the concept of a capped annuity is theoretically attractive but impossible to implement in most current healthcare systems; and second, pricing a gene therapy as a multiple of the yearly cost of expensive protein replacement therapies is considered highly artificial and unjustified.

Whereas payers understand that P&R systems may need adjustments to accommodate the specificities of gene therapies, they resist a paradigm shift in payment approach. For example, the pharmacy director of a large German sick

fund comments, "Gene therapies are like any other therapy. They will be reimbursed based on the value of their patient benefits using existing mechanisms. We will not change our health system to cover for gene therapies but will find ways to make those fit into our pricing and reimbursement processes."

We contacted 29 payers in the United States and Western Europe to survey their preferred payment method for gene therapies (Box 1). We asked payers to identify their top two choices for payment, either in a theoretical environment without health system constraints or in a real-life setting within the constraints of the health system they are working in (Fig. 1a).

Similar to other stakeholders, in the absence of health system constraints, payers prefer annuities. Annuities reduce initial financial strain, lead to predictable yearly budget impact and reflect the ongoing value of gene therapy. Capping the accrued annuities also limits overall expense. However, in the real world, approaches based on a lump sum payment represent the large majority (70%) of mentions. This shift in responses is driven primarily by the perceived lack of practicality of annuity-based payments in current health systems.

In many large pharmaceutical markets, people frequently change health plans. Transferring annuity contracts from one plan to another without an associated provision of services is currently not considered possible. Members with previous financial obligations for gene therapy would produce difficult and cumbersome claims processes. Plans could refuse patients or companies with self-funded health insurance could resist hiring new employees with ongoing annuity payments, leading to potential discrimination and associated legal clutter. Lapses in coverage might occur, leaving patients at risk of unbearable out-of-pocket payments.

To overcome these hurdles the creation of federal or regional risk pools has been proposed in various countries. However, implementation will be challenging, as illustrated by the United Kingdom where the Cancer Drugs Fund is under question, and where a Rare Disease Fund is still to be implemented. Within public health systems, long-term funding is not guaranteed and depends on political decisions. In countries with private (at least partially) and competitive health insurance markets, the definition of contributions and of coverage policies will likely create recurrent conflicts. Therefore, a lump sum payment for gene therapy remains the preferred approach in most large Western markets (Supplementary Fig. 1).