Statement of

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Before the

Subcommittee on Intellectual Property

of the

Committee on the Judiciary
United States Senate

Hearing on

THE STATE OF PATENT ELIGIBILITY IN AMERICA: PART III

June 11, 2019

Dear Chairman Tillis, Ranking Member Coons, and other members of the Subcommittee,

Thank you for the opportunity to appear before the Subcommittee at the third hearing in the series on The State of Patent Eligibility in America. I am honored to be here today to share why we believe the proposed changes you are considering will unintentionally stifle innovation and harm patient care.

Beginning with my doctorate in molecular genetics, and since, as a leader in several genetic medicine companies, I've seen first-hand how the industry has transformed since the Supreme Court decision on patents on DNA in 2013. While we understand the legislative language as released is still a proposal, I believe it poses an existential threat to future progress and respectfully request that you consider an alternative and more narrow approach.

Although there are numerous reasons to proceed with caution with modifying patent policy regarding this rapidly evolving field of genomic medicine, I would like to particularly highlight three:

1. First, the golden age of precision medicine ushered in by the unanimous *Association for Molecular Pathology v. Myriad Genetics, Inc.*, *Alice v. CLS Bank International*, and *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* decisions has just begun. Patient care has improved and innovation in genetics has thrived because of the lack of patents on DNA, not in spite of it.
2. Second, enabling patents on genetic information threatens that progress, and it is important to understand that the threat extends to other aspects of molecular diagnostics, beyond simply avoiding patents on the genes themselves.
3. And, third, if the Subcommittee believes legislation is needed to address concerns with the patent system, the proposal should also preserve what is currently beneficial to innovators, instead of indiscriminately sweeping away 150 years of case law.

We created Invitae to drive genetics into mainstream medicine by making genetic testing affordable and accessible to anyone who can benefit from it. This year, we will serve more than half a million patients -- people with cancer, with cardiovascular disease, children with rare developmental disorders, and others -- by providing information their physicians will use to tailor and personalize their care.

However, in 2012, the idea that we would be the company we are today was anything but obvious. We were turned down by hundreds of investors who said our goal to offer a comprehensive menu of the world's medical genetic tests at lower prices would never work for one reason: the DNA patent thicket. Despite the availability of the necessary technology, sequencing handfuls of genes, much less hundreds as we do today, was impossible at that time due to patents on DNA.

In the early days of Invitae, I observed medical genetic clinics at children's hospitals in the U.S., and I saw the human toll of the investors' objections on clinical care. I watched families come in with their very ill children, desperately seeking answers. It was incredibly humbling and infuriating to witness, knowing as I did that the next step in the process would be unnecessarily long, complex, and costly. I knew that the genetic counselor they were about to see had a computer monitor covered with dozens of sticky notes that listed, gene by gene, which laboratory offered testing for which gene at what cost. Sick babies and children who needed hundreds of genes tested to achieve a diagnosis were being cared for by a heroic genetic counselor who created a patchwork quilt of sticky notes to provide a comprehensive solution to her patient's testing needs. Each of those sticky notes represented a patent-holder on DNA. It may have been a small lab with a single gene test who lacked the scale or infrastructure to make testing widely available, or a large commercial lab who charged thousands upon thousands of dollars for a single gene test. Turnaround times were months or years as parents bankrupted themselves to end their child's diagnostic odyssey amid a sea of patents.

Our team was committed to finding a way to help, believing as we did that medicine that was built on the taxpayers' investment in the Human Genome Project should not be locked away in a thicket of patents. Thus, in keeping with our mission, we filed an amicus brief in 2013 on behalf of the plaintiffs in the *Association for Molecular Pathology v. Myriad Genetics, Inc.* (*AMP v. Myriad*). Our chief medical officer, Dr. Robert Nussbaum, was then Chief of the Division of Genomic Medicine at the University of California-San Francisco (UCSF), and served as an expert witness for the plaintiffs. When the *AMP v. Myriad* decision was handed down in June 2013, our young start-up company celebrated. We knew it opened a pathway for us and other innovators like us who had new ideas about how the diagnostics industry could be improved and a deep dedication to making it work better for patients and their clinicians.

#1: Post- ***AMP v. Myriad:*** **The Golden Age of Precision Medicine**

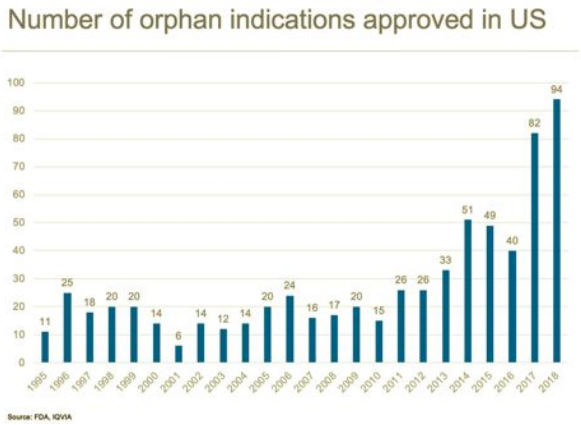
Seemingly overnight, a vibrant industry sprang up, ushering what we now see all around us - a golden age of precision medicine that has created access to better care for patients, reduced costs to the healthcare system, and increased jobs and revenue for communities.

With the patent thicket cleared, innovation from Invitae and others delivered meaningful progress. Within hereditary breast cancer alone:

- The cost of testing plummeted from $4,400 in 2013 to $250 cost to the patient at Invitae today.
- The turnaround time for results fell from months to days, which is essential for women making time-sensitive decisions about life-altering surgery.
- The single-gene testing utilized in 2013 is now known to be inferior to large multigene panels. Panel testing, as we provide at Invitae, is now the standard of care -- progress that would have been nearly impossible if licensing was required.

That progress was repeated -- and continues -- across many other conditions, from Lynch Syndrome, to pediatric epilepsy, to cardiovascular conditions and many more. That same genetic counselor I visited all those years ago today has a variety of options for those children, up to and including free testing of hundreds of genes with results available in as little as 10 days. Even if the patient has to pay, the cost per sample is $250 for a diagnostic panel that includes hundreds of genes.

Because genetic diagnosis became affordable and accessible, we've seen a corresponding boom in precision therapeutics, with gene-linked therapies at an all-time high. They are bringing hope to patients battling diseases like cystic fibrosis, non-small cell lung cancer, and even hepatitis C. The number of both applications and approvals for orphan drugs with the Food and Drug Administration accelerated significantly after 2013[1] and 2018 represented an all-time high for drug approvals overall, with orphan drugs for rare, often genetic, disorders accounted for more than half of all approvals.[2] The broad availability and low-cost of genetic sequencing is a core driver of this success.



[1] Quintiles IMS for the National Organization for Rare Disorders, Orphan Drugs in the United States: Providing Context for Use and Cost. October 2017. Available at: https://rarediseases.org/wp-content/uploads/2017/10/Orphan-Drugs-in-the-United-States-Report-Web.pdf

[2] Taylor, Phil. Orphan drugs dominate FDA's record-breaking year. PM Live. Published January 2, 2019. Available at: http://www.pmlive.com/pharma_news/orphan_drugs_dominate_fdas_record-breaking_year_1273631

Genetic testing makes is easier and faster to identify patients who may benefit from a personalized therapy, helps those patients qualify for clinical trials, and can speed time to diagnosis and treatment with currently available therapeutics.

Since 2013, a vibrant genetic testing industry has flourished, not only benefiting patients, but also the communities in which they reside. Again, we are succeeding because of the absence of patents on DNA, not in spite of it. Pre-2013, conventional wisdom was that the diagnostic genetic testing industry would never include more than 250,000 patients. Five years later, our single company has more than 1,000 employees and will provide testing to 500,000 patients just this year alone. We are not alone in this success.

Illumina, the US – based powerhouse at the center of the genomics revolution has experienced considerable growth in the past years, in large part fueled by the expanding market for sequencing for which the precedent case law has cleared room. Today, Illumina employs approximately 7,000 with $3.3 billion in revenue.

Illumina – Key statistics

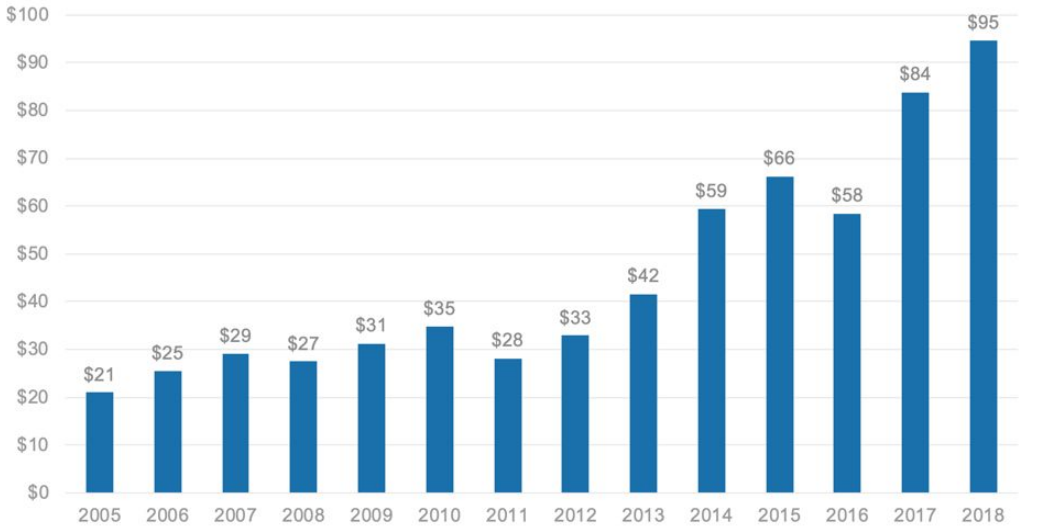
$mm, except per share data	2014	2015	2016	2017	2018
Net Sales or Revenues	1,861.4	2,219.8	2,398.4	2,752.0	3,333.0
Growth	30.97%	19.25%	8.05%	14.74%	21.11%
Cost of Goods Sold	451.1	544.1	591.0	752.0	854.0
% of Sales	24.23%	24.51%	24.64%	27.33%	25.62%
Gross Profit	1,297.7	1,549.3	1,666.4	1,844.0	2,300.0
Gross Margin	69.72%	69.80%	69.48%	67.01%	69.01%
Selling, General & Admin Expenses	850.1	926.2	1,087.4	1,215.0	1,417.0
% of Sales	24.90%	23.64%	24.31%	24.49%	23.82%
EBITDA	603.1	751.7	735.3	1,236.0	1,130.0
EBITDA Margin	32.40%	33.86%	30.66%	44.91%	33.90%
Operating EBITDA	560.2	749.5	719.9	785.0	1,062.0
Operating EBITDA Margin	30.10%	33.77%	30.02%	28.52%	31.86%
EBIT	490.5	625.3	594.4	1,080.0	951.0
EBIT Margin	26.35%	28.17%	24.78%	39.24%	28.53%
Operating EBIT	447.6	623.1	579.0	629.0	883.0
Operating EBIT Margin	24.05%	28.07%	24.14%	22.86%	26.49%
Pretax Income	448.8	583.1	561.2	1,043.0	894.0
Pretax Margin	24.11%	26.27%	23.40%	37.90%	26.82%
Net Income to Common Shareholders	353.4	461.6	462.6	876.0	837.0
Net Margin	18.98%	20.79%	19.29%	26.38%	24.78%

Price per share	$318.56
Market capitalization	$46,766.6
Cash	$3,512.0
Debt	$1,997.0
Enterprise value	$45,251.6
2018 EV/Revenue[1]	12.7x
2018 EV/EBITDA[1]	37.6x

Source: ThomsonOne; market data as of 6/6/19
[1] As of 12/31/18

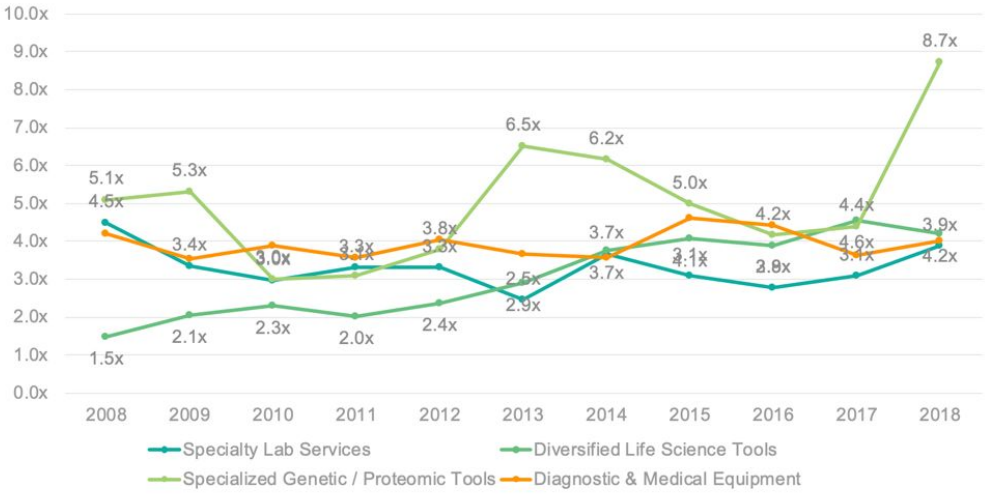
Similarly, companies in life sciences and diagnostics have been increasing in value significantly since 2013, with genetic medicine companies outpacing the rest.

Precision Medicine cumulative market cap ($bn)

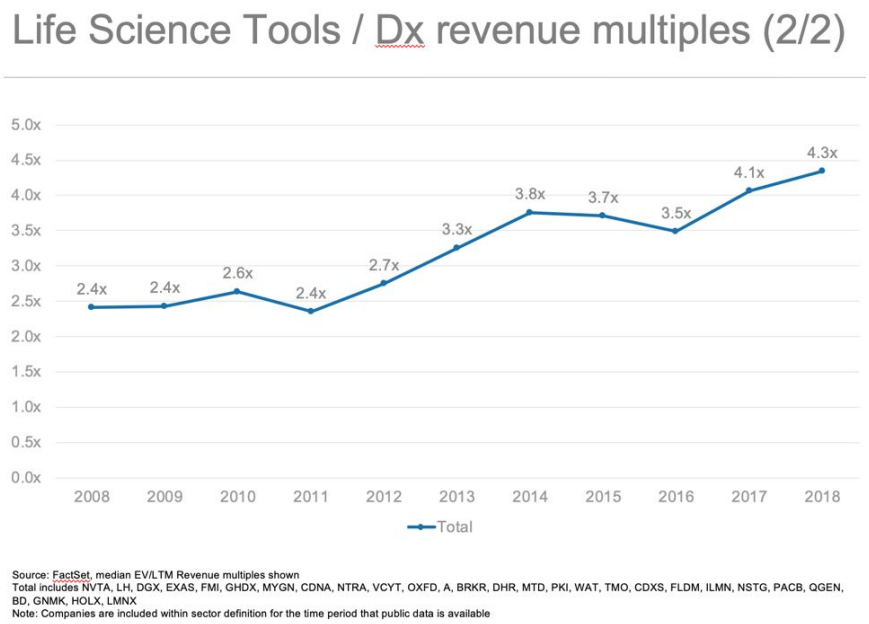


Source: FactSet
Includes NVTA, LH, DGX, EXAS, FMI, GHDX, MYGN, CDNA, NTRA, VCYT, OXFD, CDXS, FLDM, ILMN, NSTG, PACB, QGEN
Note: Companies are included within sector definition for the time period that public data is available

Life Science Tools / Dx revenue multiples (1/2)



Source: FactSet, median EV/LTM Revenue multiples shown
Specialty Lab Services includes NVTA, LH, DGX, EXAS, FMI, GHDX, MYGN, CDNA, NTRA, VCYT, OXFD
Diversified Life Science Tools includes A, BRKR, DHR, MTD, PKI, WAT, TMO
Specialized Genetic / Proteomic Tools includes CDXS, FLDM, ILMN, NSTG, PACB, QGEN
Diagnostic & Medical Equipment includes BD, GNMK, HOLX, LMNX
Note: Companies are included within sector definition for the time period that public data is available

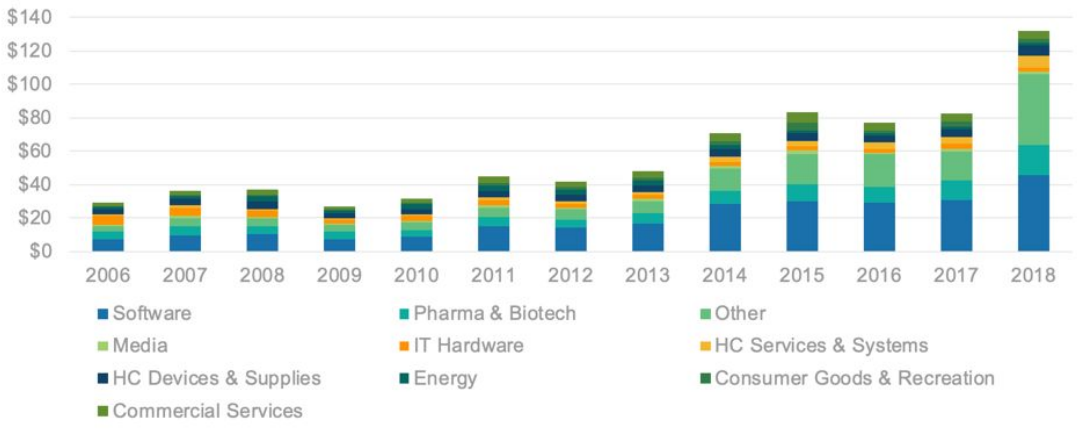


Source: FactSet, median EV/LTM Revenue multiples shown
Total includes NVTA, LH, DGX, EXAS, FMI, GHDX, MYGN, CDNA, NTRA, VCYT, OXFD, A, BRKR, DHR, MTD, PKI, WAT, TMO, CDXS, FLDM, ILMN, NSTG, PACB, QGEN, BD, GNMK, HOLX, LMNX
Note: Companies are included within sector definition for the time period that public data is available

Investors have recognized the value being created by these companies and have responded with further investment to fuel innovation. By 2018, investment in the sector had increased dramatically, from $6.21 billion in 2013 to $17.72 billion in 2018. Our company and others focused on genetic testing were able to raise capital during this time period to fund research and development and grow our organizations -- all providing greater access to genetic testing and helping to accelerate the adoption of precision medicine for patients.

Venture capital investment by sector ($bn)

$bn	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Software	7.28	9.55	10.06	7.31	8.46	15.43	13.90	16.71	28.60	29.83	29.41	30.56	45.91
Pharma & Biotech	4.37	5.57	4.85	4.87	4.60	4.90	4.98	6.21	7.48	10.50	8.93	12.07	17.72
Other	3.17	4.47	4.68	3.54	4.00	5.93	6.17	6.77	13.45	18.02	19.54	17.33	42.33
Media	0.80	1.44	1.32	0.75	0.83	1.59	1.09	1.69	1.60	2.03	1.48	1.62	1.48
IT Hardware	5.45	4.82	3.64	2.48	3.12	2.87	2.50	2.43	2.09	2.49	1.83	2.58	2.51
HC Services & Systems	1.09	1.44	0.95	0.83	1.27	1.24	1.67	1.95	3.35	3.45	4.15	4.17	7.02
HC Devices & Supplies	2.99	4.04	4.40	3.05	3.19	3.92	3.68	3.98	4.78	4.46	3.63	4.95	5.99
Energy	1.32	1.94	3.12	1.96	2.82	3.69	2.94	2.57	2.01	1.51	1.56	1.12	1.69
Consumer Goods & Recreation	0.69	0.41	0.89	0.51	0.56	1.64	1.85	1.46	2.43	4.56	2.06	3.37	2.73
Commercial Services	2.02	2.33	2.93	1.86	2.43	3.67	2.74	4.03	5.19	6.14	4.42	5.09	4.71
Total VC	29.18	36.01	36.84	27.16	31.28	44.87	41.52	47.81	70.99	82.99	77.01	82.86	132.09



Source: NVCA 2019 Yearbook

Competitors – Revenues / Investment

Revenues ($mm)

Company	2011	2012	2013	2014	2015	2016	2017	2018
Natera			$55	$159	$190	$213	$210	$258
Counsyl						$93	$112	$138

Natera investment ($mm)

Round	Raised	Date
Series A	$4	12/5/07
Series B	$6	1/8/09
Series C	$12	11/2/10
Series D	$20	1/6/12
Series E	$55	5/1/13
Series F	$56	4/6/15
IPO	$180	7/1/15
Follow-on	$90	7/12/18
Follow-on	$100	4/17/19
Total	**$522**	

Counsyl investment ($mm)

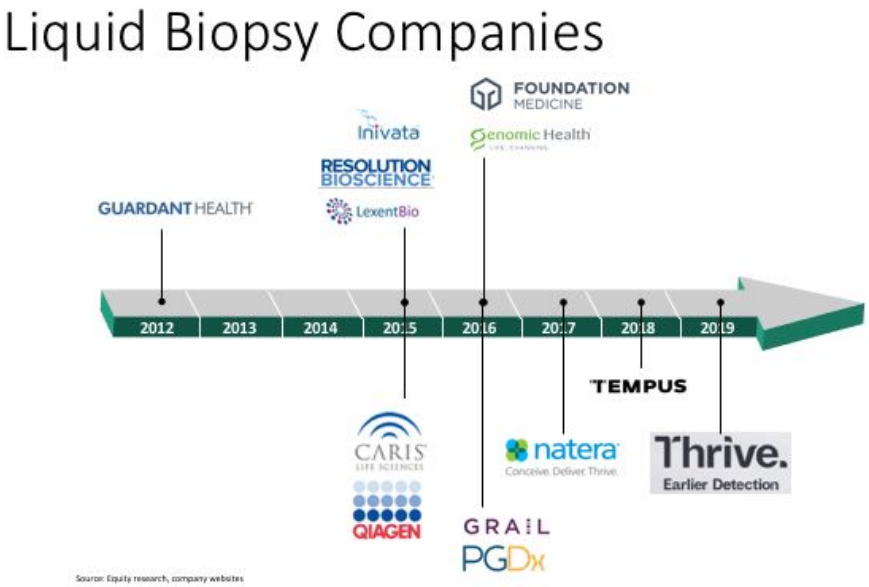
Round	Raised	Date
Series A	$8	4/13/09
Series B	$36	3/16/10
Series C	$9	8/24/12
Series D	$42	5/8/14
Debt	$40	8/1/15
Debt	$80	11/6/17
Total	**$214**	

Progenity investment ($mm)

Round	Raised	Date
Series A	$2	1/9/12
Mezzanine	$14	6/27/13
Series A	$12	8/16/16
Series B	$125	11/7/17
Total	**$153**	

Source: Company websites, SEC filings, Pitchbook
Note: Progenity revenues and Integrated Genetics revenues/invested capital not available due to private company status; Integrated Genetics subsidiary of LabCorp

Another example demonstrating rapid innovation in diagnostics is the liquid biopsy market, which has similarly seen rapid uptick in entrants since the 2013 decisions.



Ultimately, this impact of investment and a vibrant start-up landscape is to create competition that helps increase choice and drive costs down. It was reported in early 2018, that over 70,000 genetic tests were available to patients and the growth in the availability of genetic testing is accelerating with an average of 14 tests entering the market per day.[3] As the authors of the 2018 publication point out, a substantial portion of these tests are comparable to each other indicating that competition in this field is alive and well. In particular, this is true for multi-gene panels which were difficult to construct before *AMP v. Myriad*. In fact, the authors find that between January 2014 and March 2018, the number of multi-gene panels that include *BRCA1* and *BRCA2* grew ten-fold -- at the time of the report's release, there were 374 genetic tests that included these once-patented genes. Moreover, the cost of hereditary breast and ovarian cancer testing has plummeted from over $4,000 to a cost of $250 to the patient today at Invitae. The wait time for results similarly plummeted, from months to 10-21 days in our lab. We now understand that single-gene testing is inferior to the use of large multi-gene panels in cancer testing, which has become standard care -- progress for patients and healthcare providers depending on the best available information to enable them to make care management decisions would have been slowed by gene-by-gene licensing.

As a result of these advancements, more patients are able to obtain testing and research findings are quickly translated into improved medical care. Data was published in December 2018 in the Journal of Clinical Oncology[4], showing that current testing guidelines in hereditary breast cancer were too narrow in that they missed as many patients with actionable variants as they identified. Professional guidelines from the American Society of Breast Surgeons released in February 2019 specifically cited cost reductions as a factor in their recommendation to expand testing to all breast cancer patients.[5]

The benefits of the *AMP v. Myriad* decision are not limited to cancer testing; other successes include childhood epilepsy, early childhood retinal degeneration (retinitis pigmentosa), critically ill neonates in the NICU, and children with undiagnosed developmental problems and intellectual disabilities. For example, genetic testing for childhood epilepsies has historically cost thousands. Today we offer testing for $250 to the patient. In addition, we are one of five partners in a program known as Behind the Seizure in which sponsors underwrite the cost of

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[3] Concert Genetics. The current landscape of genetic testing: Market growth, reimbursement trends,challenges and opportunities. http://www.concertgenetics.com/wp-content/uploads/2018/04/12_ConcertGenetics_CurrentLandscapeOfGeneticTesting2018.pdf. Published March 2018. Accessed June 8, 2019.

[4] **Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle?**. Beitsch, P., Whitworth, P., Hughes, K., et al. Journal of Clinical Oncology 2019 37:6, 453-460 Available at: https://ascopubs.org/doi/10.1200/JCO.18.01631

[5] American Society of Breast Surgeons Consensus Guideline on Genetic Testing for Hereditary Breast Cancer. Available at https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf

testing so it can be offered at no charge to any child under 60 months old who has experienced an unprovoked seizure. Since the program began, hundreds of children have received genetic testing through Behind the Seizure and research has shown participants in the program were diagnosed 1-2 years earlier than historic averages.[6] This program within epilepsy is just one of more than 30 such programs our company offers that helps make no-charge testing available to patients in an effort to increase access and support earlier diagnosis.

For patients where the diagnosis is not apparent, many healthcare providers find whole genome or exome sequencing is the best approach for deriving medically actionable results. Whole genome or exome sequence depends on being able to scan large numbers (up to 20,000) genes to find a change responsible for a condition. In the post-*AMP v. Myriad* world, the number of laboratories offering whole exome testing grew nearly 75% between January 2016 and March 2018[7], and the cost of whole genome sequencing has dropped dramatically in recent years. We are quickly approaching the goal of a $1,000 genome. Recognizing the utility of whole genome analysis and the reduction in cost, in 2018, Congressman Swalwell introduced H.R. 5062: The Advancing Access to Precision Medicine Act to provide Medicaid coverage for whole genome analysis for children without a diagnosis in pediatric intensive care units. If patents on DNA sequences existed, the cost would be dramatically higher and policymakers may find expanding access to these services out of reach for lower-income patients.

It is clearly contrary to the best interests of patients and medical care to have a situation in which patents on DNA require that in order to have a whole genome or exome sequence analysis, hundreds to thousands of licensing agreements would have to be obtained or purchased or, even worse, a molecular pathology professional would be prohibited from interpreting and reporting harmful variants from that gene even though they may be medically relevant to that patient.

Today, breakthroughs in precision therapeutics can be more quickly adopted due to the availability of diagnostics to accelerate clinical trials and to provide diagnostics once on-market. The number of precision medicines on the market continues to grow and the Personalized Medicine Coalition reports that precision medicines accounted for more than 30% of the approvals for in 2017 at the U.S. Food and Drug Administration.[8] One report from 2015 indicates that 42% of drugs in development are precision medicines and found that

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[6] Miller, Nicole, et al, "Behind the Seizure: A No-Cost 125-gene Epilepsy Panel for Pediatric Seizure Onset Between 2–4 Years". Presented at the American Society of Human Genetics Meeting: October 16–20, 2018, San Diego, CA.

[7] Concert Genetics. The current landscape of genetic testing: Market growth, reimbursement trends,challenges and opportunities. http://www.concertgenetics.com/wp-content/uploads/2018/04/12_ConcertGenetics_CurrentLandscapeOfGeneticTesting2018.pdf. Published March 2018. Accessed June 8, 2019.

[8] The Personalized Medicine Coalition. Personalized medicine at FDA: 2017 Progress Report. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_2017_Progress_Report.pdf. Accessed June 8, 2019.

biopharmaceutical firms had been expecting to substantially increase their investments.[9] Laboratory tests will have a vital role in their development and use in the clinical setting.

#2: Abrogating Recent Unanimous Supreme Court Decisions will Lock Up Innovation in Precision Medicine

We are fortunate in that we have the option to review the state of innovation and the industry before and after the Supreme Court decisions to better understand the consequences of a legislative proposal that would abrogate all court decisions. Innovations used in the clinical setting rest upon the foundational knowledge gained through research, and we know from history that gene patents were, and would be, an impediment to scientific research. The members of this Subcommittee are likely well aware of the importance of the Human Genome Project and the tremendous shift that resulted in medicine with the successful completion of the grand challenge. One interesting aspect of the Human Genome Project is the infamous story regarding the competition between the federally supported public effort and the private entity Celera. Celera's efforts ended in 2001 when they published a partial sequence of the human genome[10], and subsequently, they were able to obtain intellectual protections on the genes not yet sequenced by the public effort. In a report from 2013, Williams describes that these protections allowed Celera to control licensing for using and commercializing innovations involving those genes which allowed Williams to compare the subsequent research and development between Celera's protected genes and those genes able to be freely studied as a result of the Human Genome Project.[11] Making use of this unique situation, Williams found that Celera's intellectual protections resulted in a 20 to 30 percent decrease in scientific research and product development.

A more complete assessment by the U.S Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) in 2010, through the evaluation of the available evidence and original case studies of genetic testing for 10 clinical conditions including inherited susceptibility to breast/ovarian cancer, colon cancer and Alzheimer's disease, similarly found that patents negatively impacted research and/or caused a disruption in patient access to other sources for testing.[12] Overall, this esteemed group of thought leaders

[9] Tufts Center for the Study of Drug Development. Personalized medicine gains traction but still faces multiple challenges. Impact Report. 2015;17(3).

[10] Venter JC, Adams MD, Myers EW, et al. The Sequence of the Human Genome. Science (80-). 2001;291(5507):1304-1351. doi:10.1126/science.1058040

[11] Williams, H. Intellectual Property Rights and Innovation: Evidence from the Human Genome. Journal of Political Economy. 2013;121(1):1–27. https://economics.mit.edu/files/8647

[12] Secretary's Advisory Committee on Genetics, Health, and Society, Department of Health and Human Services. Gene patents and licensing practices and their impact on patient access to genetic tests. https://osp.od.nih.gov/wp-content/uploads/2013/11/SACGHS_patents_report_2010.pdf. Published April 2010. Accessed June 7, 2019.

concluded that patents "do not appear to be necessary for either basic genetic research or the development of available genetic tests." Of particular interest for those working to advance precision medicine, the SACGHS noted that the world in which gene patents were allowed did not lead to faster development of a test and additionally, they specifically expressed concern about patents being a significant barrier to the creation of the exact kind of comprehensive multi-gene panels that are now offered by Invitae and others. The members of the SACGHS recognized the burden associated with negotiating numerous licenses and how the cost of these endeavors may render a test that is quite valuable from a clinical perspective, otherwise not worthy of the financial investment. This point is especially relevant because of how many conditions are polygenic in nature, including the three examples illustrating the impact of patents on commercialization I provide below: testing for large rearrangements in *BRCA*; long QT syndrome testing; and, genetic testing for Lynch syndrome.

Prior to the *AMP v. Myriad* decision, the lag between clinical research and commercialization was long. There are numerous techniques and approaches used to collect the most comprehensive and meaningful information for patient care. In the case of hereditary breast and ovarian cancer genetic testing, it has been known since 1999 that large rearrangements in *BRCA1* is likely responsible for approximately 10% of all disease-causing mutations.[13] Yet, the company holding exclusive testing rights under their patent originally used a testing approach (shortrange polymerase chain reaction followed by genomic sequencing) that only accounted for the five most common types of rearrangements in the *BRCA1* and *BRCA2* genes, and thus, the test that launched in 2002 potentially missed 12% of genomic rearrangements that can be detected using other technology.[14] It took another four years for a test accounting for all known large rearrangements to be made available, and it has been speculated that this was only in response to pressure from the scientific community to improve the methodological approaches in clinically offered tests.[15] During that time, it remains unknown how many families may have received false negative results and subsequently, missed opportunities to diagnose their cancer early or prevent it altogether.

This kind of lag was also an issue in the development of genetic testing for familial long QT syndrome, an inherited heart rhythm disorder that can lead to sudden cardiac death. Without testing, families often only learn they have this disease in their family when a relative dies from sudden cardiac arrest, especially after taking a QT-prolonging drug that they and their

[13] Puget N, Stoppa-Lyonnet D, Sinilnikova OM, et al. Screening for germ-line rearrangements and regulatory mutations in BRCA1 led to the identification of four new deletions. Cancer Res. 1999;59(2):455-461. http://www.ncbi.nlm.nih.gov/pubmed/9927062.

[14] Walsh T, Casadei S, Coats KH, et al. Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer. JAMA. 2006;295(12):1379. doi:10.1001/jama.295.12.1379

[15] House Judiciary Committee, Subcommittee on the Courts, the Internet and Intellectual Property; oversight hearing on Stifling or Stimulating?—The role of gene patents in research and genetic testing. October 30, 2007 See Appendix A, supplementary written statement from Dr. Wendy Chung, Columbia University.

physicians would have been counseled to avoid had they known the mutation was present. Some of the relevant genes to familial long QT syndrome were patented by the University of Utah as early as 1997 (U.S. 5599673), which granted a license to their patents shortly after. However, licensing was done in such a fragmented way that lab skirmishes[16] and other delays in bringing tests to market contributed to the significant delay (approximately 9 years) between the granting of the first patent and the commercialization of more comprehensive multi-gene testing in 2004.[17] It was yet another two years before a second lab was able to secure a license to offer testing. Throughout this period, patients had no option to obtain this needed testing from the license holders, and even when testing became available from competitors, the license holders prevented patient access by taking legal action against those laboratories. Furthermore, when testing was introduced in 2004, according to a report from the Secretary's Advisory Committee on Genetics, Health, and Society in 2010, it cost $5,400.[18] Today, in the post-*AMP v. Myriad* era, Invitae offers panel testing for familial Long QT syndrome at a cost of $250 to the patient.

Conversely, during roughly the same time period, genetic testing for Lynch syndrome illustrated testing could be brought forward to help patients more quickly without patent enforcement. Lynch syndrome is a hereditary syndrome with high risk for developing colon, uterine, ovarian and other types of cancer. It is just as common as Hereditary Breast and Ovarian Cancer syndrome and making a diagnosis is just as impactful for patient care. Two of the genes most commonly implicated in the syndrome were patented (U.S 5922855 and U.S. 5591826) in the late 1990s by two different entities. Thus, performing adequate Lynch testing would have required licensing from both the entities. Fortunately, licensing was not exclusive and, in fact, the holders of the patents never enforced them. We now understand that there are five genes implicated in Lynch syndrome, and taken to its logical conclusion, the testing panel currently recommended by all professional clinical guidelines[19] could theoretically have required five different licensing agreements before the *AMP v. Myriad* decision. Such an arrangement is not only clumsy, it is totally unnecessary as demonstrated by the rapid adoption of comprehensive Lynch syndrome gene panel testing by multiple providers without patent protection.

Because the patents were never enforced, the commercialization of Lynch syndrome testing was successful and rapid. In 2008, compared to one company providing testing for hereditary

[16] Feature Story: A case of limited clinical access. Cap Today, February 2010. Available at: http_www.captodayonline.com_Archives_0210_0210ab_limited_clinical_access.pdf

[17] Angrist, M., et al. Impact of gene patents and licensing practices on access to genetic testing for long QT syndrome. Genet Med 2010:12(4):S111–S154.

[18] Secretary's Advisory Committee on Genetics, Health, and Society, Department of Health and Human Services. Gene patents and licensing practices and their impact on patient access to genetic tests. https://osp.od.nih.gov/wp-content/uploads/2013/11/SACGHS_patents_report_2010.pdf. Published April 2010. Accessed June 7, 2019.

[19] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2018

breast cancer, at least nine laboratories were offering testing for Lynch syndrome providing patients with choice and allowing laboratories to compete by making improvements to quality, turnaround time, convenience, and cost.

Today the sequence of all genes in the human genome is known and publicly available. The sequence as posted in public databases, and the millions of variants posted on public databases, are in the public domain and learning that data does not require any creative patentable process. Perhaps more importantly, the accelerating progress towards truly personalized medicine over the last several years shows that the economic incentives associated with improved healthcare are motivating industry participants without needing the added incentive of the patent owner's exclusionary rights.

Since *AMP v. Myriad*, there has been a publicly driven effort supported by researchers and genetic testing laboratories to share and provide open access to information on genetic variants. In 2017, the American College of Medical Genetics and Genomics published a statement on data sharing, noting that "Information that underpins health-care service delivery should be treated neither as intellectual property nor as a trade secret when other patients may benefit from the knowledge being widely available."[20] The American Medical Association offered a similar view in 2013. We are among the largest contributors of information on clinically observed genetic variants to the ClinVar project, an effort by the National Center for Biotechnology Information (NCBI) to aggregate all of the world's known relationships between genetic variants and disease. ClinVar is a freely available archive of submissions from across the world of variants and their interpretations by the lab that observed them. We have submitted observed variants to ClinVar throughout our history and as of today are the second-highest submitter, with total submissions of more than 173,500.[21,22]

By freely contributing information on genetic variants found in our clinical testing and the underlying reasoning behind how these variants are interpreted, we can help increase the quality and utility of genetic data available to the research and clinical communities as a whole. By sharing de-identified variants with public databases, we support the appropriate gold standard of expert consensus, open peer-review, and detailed inter-laboratory quality control. We believe the only responsible medical practice is to share de-identified data to improve overall genomic healthcare. We want clinicians and researchers to be able to compare variants across multiple platforms and fully utilize the available data through unified resources. ClinVar has catalyzed efforts across laboratories to better understand gene-disease associations,

[20] American College of Medical Genetics and Genomics Board of Directors, "Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics."Genetics in Medicine January 5, 2017. https://www.nature.com/articles/gim2016196
[21] CinVar Submitter List. Accessed June 8, 2019. Available at: https://www.ncbi.nlm.nih.gov/clinvar/docs/submitter_list/
[22] Invitae data on file.

continually improve reporting guidelines, and collaborate in cross-laboratory quality control programs. These efforts will contribute to improving healthcare for all patients.

Should associations between observed variants and disease once again become patentable, this type of data sharing would come to a standstill, dramatically slowing the pace of precision medicine research and harming the quality of genetic variant interpretation industry-wide.

Turning attention to cost, genetics companies are today pursuing a different model for healthcare -- although common in other industries -- where there are no patents and the focus is on reducing the cost per test and improving service. This provides a model that would have benefits for the healthcare system as a whole. We have seen the opposite effect with the impact of drug patents on health care costs. Research has shown the biggest drivers of increasing healthcare costs since 2017 has included fewer drug patent expirations.[23] A return to gene patents -- whether explicitly or in practical effect -- will reverse the progress in this sector of healthcare and threaten to turn genetic testing into another area of medicine dominated by high-margin businesses.

From a public health perspective, high-cost genetic testing would dramatically slow the goals of Congressionally supported programs such as the National Institutes of Health's All of Us program, which seeks to gather genetic information from more than one million Americans in an effort to accelerate research and uncover paths toward delivering precision medicine. Another program supported by Congress, the National Cancer Institute's Cancer Moonshot program, has a core focus on hereditary cancers, noting that the use of genetic screening for the more than 50 hereditary cancers remains "a vastly underutilized cancer prevention strategy" due to both cost and access to testing.[24]

Some of the witnesses at the first two hearings suggested that DNA isolated outside the body or a segment of DNA, perhaps a particular variant, would be patentable under your proposed legislation. They attempted to draw a distinction between genes inside the body and genes isolated; however, scientifically, this distinction does not exist. In his expert witness testimony to *AMP v. Myriad*, our Chief Medical Officer, Dr. Nussbaum, explained that when isolating a DNA segment of interest, neither extracting total cellular DNA nor separating a particular DNA segment away from the rest of DNA produces a substance that is "structurally distinct from any substance found in the human body". Instead, an isolated DNA segment, as DNA, is not significantly different from the same segment of DNA in the cellular DNA from which it was derived. Further, any differences between isolated DNA and DNA in chromatin are actually

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[23] https://www.healthsystemtracker.org/chart-collection/recent-forecasted-trends-prescription-drug-spending/#item-contribution-to-growth-in-drug-spending-by-growth-driver_2017

[24] National Cancer Institute Cancer Moonshot Website. Available at: https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/hereditary-cancers

"epigenetic" changes (note, they are not "genetic"), which means they are superimposed upon genes and not part of a gene itself.

Additionally, while technology can be used to break the covalent bonds between DNA base pairs in a laboratory setting, this same process occurs naturally within the body and hence, does not result in novel DNA. The Supreme Court decision in *AMP v. Myriad* affirmed this as well rendering all naturally occurring genetic sequences as not being eligible for patent protection. Also unpatentable were tools such as probes that were specifically designed to detect a newly discovered, but naturally occurring mutation. Prior to 2013, there were 3,000-5,000 genes whose sequence was patented for the purpose of creating nucleic acid products used for genetic analysis, e.g. primers or probes for diseases caused by alterations of genetic material. If the *AMP v. Myriad* decision were overruled somehow, then patents on these materials would further create barriers to innovation in precision medicine and patients' access to testing.
We are extremely concerned for the reasons outlined above that the draft legislation would leave open the possibility that isolated forms of DNA segments could be patented if the language becomes law, stunting the precision medicine field.

There are thousands of variants in *BRCA* that are linked to breast, ovarian, prostate, pancreatic and other cancers and many variants for which clinical significance and utility are yet to be fully understood. As the Subcommittee understands well, *Mayo Collaborative Services v. Prometheus Laboratories* (*Mayo v. Prometheus*) case held that observed connections between, on the one hand, a physical trait such as a genetic mutation or how you metabolize a drug and, on the other hand, a heightened risk of cancer or the need for a dose adjustment for a drug is in effect a "natural law." The Supreme Court found these natural law observations to be not patentable, and yet, the draft language would overturn this decision and does not otherwise protect the discovery of these associations from being patentable. Allowing patents on a specific variant and its association with disease could easily make it impossible to sequence and provide information to patients about even a single gene. Additionally, the claim that the native sequence existing in the public domain protects genes from being patented is flawed in that there is no such thing as a native sequence-- we all have variants that make us unique. An individual has a right to know their genetic information without having to pay anyone a licensing fee or be forbidden from learning some aspects that may benefit their health because of a patent.

Thus, any legislation that abrogates *AMP v. Myriad*, will not only create barriers to research, but also to innovation in precision medicine and ultimately, patient care.

#3: A Path Forward: Preserve Existing Benefits of Patent Case Law through Thoughtful Policy Development

Non-invasive prenatal screening (NIPS, sometimes referred to as NIPT) uses cell sorting technologies to obtain cell-free fetal DNA circulating in maternal blood. The breadth and robustness of the NIPS market is a direct result of court decisions including *Mayo v. Prometheus*. The investment into this critical area of care for the 6 million women per year in the US who conceive has been dramatic after each court decision with five new entrants in the last four years alone.

Furthermore, cases in this area reveal that the legal system is working as intended and patents are decided, on their facts, on a case by case basis, as they always have been, and the Supreme Courts's *Alice v. CLS Bank International* and *Mayo v. Prometheus* cases have not caused the wholesale confusion and disruption that some stakeholders are alleging. Considering just one area of NIPT litigation and a single Judge in a single court - Judge Susan Illston of the United States District Court for the Northern District of California:

In 2017, Judge Illston found several Illumina NIPS patents valid and infringed by Roche and Ariosa, awarding the plaintiff $26.7M in damages. Fast forward a year to December 2018 and the same Judge Illston, in an entirely different case featuring different NIPS patents, granted summary judgment to the defendants, finding that two patents were invalid under 101, citing *Mayo v. Prometheus*. One of those patents contained claims "that specifically focus on procedures to separate fetal and maternal DNA in a blood sample." In this case, the owner of that patent was Illumina and the defendant, Roche/Ariosa – a very real and relevant example of post-*Mayo v. Prometheus* law being applied appropriately on a case-by-case basis.

Another case worth considering, *Roche v. Cepheid*, is important as its existence does not support the argument that legislation is desperately needed immediately to rescue genetic diagnostic patents from bad section 101 case law. Instead, the litigation record in the *Roche v. Cepheid* case along with the USPTO patent grants in this field, shows that patent practitioners are actively pushing the patentability boundary when it comes to the use of genetic information in diagnostics. In turn, the courts are analyzing the patentability arguments carefully, but certainly not monolithically.

The U.S. Court of Appeals for the Federal Circuit (CAFC) in *Roche vs Cepheid* held that merely designing and isolating complementary primers for use to isolate or otherwise detect DNA in a sample is patent ineligible. The court rejected Roche's argument that while the DNA of the bacterium at issue is circular, the primers they created were linear and contained a unique chemical "end" which made them “chemically and structurally distinct from any nucleic acid that occurs in nature or that can be isolated from naturally occurring DNA.” The court also rejected

Roche's argument that the claimed primers could hybridize to “only one of eleven position-specific signature nucleotides” on the bacterium's DNA. Citing the Supreme Court *AMP v. Myriad* decision, and the later interpretation of that ruling in the CAFC's *BRCA1* case, the court ruled that the nucleotide sequences were naturally occurring and therefore patent ineligible.

The opinion of the Federal Circuit in *Roche v. Cepheid* distinguished the case of *Vanda Pharmaceuticals* (*Vanda*) which the Federal Circuit had decided just a couple of years earlier. In *Vanda* the court held that methods of treatment were eligible because they claimed a new way of using an existing drug that was safer for patients.

This holding clearly left a large opening for method of treatment claims. Lawyers and legal scholars alike have noticed the same thing: "The distinction made between the method claims in *Vanda* and in *Roche v. Cepheid* suggest that the claims of the [primer sequence in the *Roche v. Cepheid* case] *could have been eligible if they recited a method of treatment comprising first testing a sample using DNA amplification and then treating a patient with antibiotics.* Further, the court indicated that it was not expressing an opinion as to eligibility of method claims that “exploit” DNA in for “drug-like new applications.”[25]

We present the above as clear evidence of a “vigorous and real-time " debate, hardly screaming out for immediate legislative intervention

As we approach the 20 year anniversary of the Human Genome Project, our goal over the next few years should be to continue to move forward at a rapid pace instead of returning to a genetic medicine landscape partitioned into countless patented sections. We are not close to fully understanding the human genome. Thus, there will be substantial activity in this space for a long time to come. If this knowledge is privatized through patents, it will impede progress of research and delivery of precision medicine for many years—at least in the U.S.

That is why I come to you as a business leader and a geneticist deeply concerned about the legislation you are considering. Within genetics -- and despite the best of intentions -- I believe the proposed approach is fundamentally at odds with both innovation, improved patient care and public health interest. We acknowledge the need to reform aspects of the Patent Act and support your work toward that goal. However, we cannot support this draft legislation as written because it clearly will abrogate the *AMP v. Myriad* decision without making clear that a naturally occurring DNA segment, whether residing in the human body or in an isolated form, is a product of nature and thus, unable to be patented. We appreciate the numerous statements clarifying that the intent of the draft language is not to allow for patents on genes. However, even legal and patent expert witnesses at the first two hearings gave varying opinions about

[25] See "A Pathway to DNA Primer Patentability." Harvard Journal of Law and Technology. 2018.

whether the language as written supports this intent. We respectfully request that the Subcommittee work to greatly clarify the language to protect all forms of naturally occurring DNA segments from being patented and make that language so explicit.

Given the potential practical effect of this legislation would be the same as overturning *AMP v. Myriad, Mayo v. Prometheus,* and other decisions, precision medicine companies would face a new patent thicket, just as impenetrable as the one we faced six years ago. As you consider ways to modify the draft legislation, I urge you to factor in the complexity of the field of genomics and naturally occurring genetic information and examine the state of genomic research and genetic testing innovation both before and after the *AMP v. Myriad* decision to better understand the unintended consequences of any legislative proposal.

The 21st century is and will be the century of precision medicine. Right now the U.S. is a leader in this field. No small part of that fact is due to the Supreme Court's jurisprudence which has denied patent subject matter eligibility to patents that preempt the detection and interpretation of people's own genetic information. Part of the reason for the explosion of research activity in genomics is the dramatically falling price of sequencing technology. In thirty years, we have gone it taking a decade to sequence the human genome at a cost of $3 billion to being able to do so for less than $1,000 in a few days. Many of the innovations that have made this revolution possible were invented by American innovators and are patented. The Supreme Court case law on patent subject matter eligibility hasn't impaired the ability to patent the machines, platforms, reagents, and methods for new genetic sequencing technology. Innovation continues in this field at a furious pace. As an entrepreneur, I believe in the importance of the proper use of patents to drive innovation, and as I've stated earlier, patents on DNA have the opposite effect. The proposed legislation would imperil American leadership in this field.

We believe current case law has conferred substantial public and private benefits, increasing both patient access to testing and the industry's ability to create innovative, successful businesses providing it. However, if the Subcommittee believes that the law on patent subject matter eligibility is better addressed by a statute enacted by Congress, the right thing to do is to start by codifying the existing case law on patent subject matter eligibility and working to improve their clarity. The prudent and conservative approach is to start where the law is and preserve all of its beneficial features. The proposal for wholesale abrogation of Supreme Court jurisprudence on patent subject matter eligibility will have a dramatic and negative effect on the field of precision medicine as it will substantially decrease innovation and investments.

Thank you again for the opportunity to testify today -- we look forward to working with the Subcommittee as you continue to explore ways to improve the patent system. I offer my and my company's assistance as you consider modifications to current patent policy and their potential impact on precision medicine.

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