September 7th, 2021

Andrew Hirshfeld
Commissioner for Patents
Performing the Functions and Duties of the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office
600 Dulany Street
Alexandria, VA 22314

Comments submitted electronically via www.regulations.gov to docket number PTO-P-2021-0032

Dear Commissioner Hirshfeld,

Thank you for the opportunity to respond to the Request for Information for the Patent Eligibility Jurisprudence Study (docket number PTO-P-2021-0032). Invitae is the fastest-growing clinical genetics company in the United States. Our mission is to bring comprehensive genetic information into mainstream medicine to improve healthcare for patients while at the same time make testing affordable and accessible to those who can benefit from it. Our success in providing critical genetic information to over two million patients was made possible by the current patent eligibility jurisprudence in the United States. We agree with recent Supreme Court decisions that biomarkers, including DNA, and their association with a health status are naturally occuring phenomena and natural laws, respectively, and hence, are not patent eligible. Indeed American leadership in the explosive growth of the modern clinical genomics industry has benefited greatly from current patent eligibility jurisprudence which wisely precludes patenting the human genetic code and its interpretation.

We are concerned about the approach taken in the Request for Information, which may influence the types of responses you recieve. The questions are posed with the underlying assumption that recent jurisprudence has resulted in negative outcomes for industry, competitive disadvantages for the United States, and consequences for patient care. We believe that the premise is inaccurate and the structure of the Request for Information will fail to elicit a balanced response reflective of the full scope of reactions to current patent eligibility jurisprudence. We encourage future engagement with stakeholders from a more neutral position on the impact of patent eligibility jurisprudence to invite those who have experienced financial growth, competitive advantage, and improved patient outcomes to respond.

In fact, there is significant evidence that recent patent eligibility jurisprudence has led to unprecedented growth in both the precision medicine and molecular diagnostic fields. More

© 2021 Invitae Corporation. All Rights Reserved.

specifically, it has ushered in a rich diversity of companies offering a wide range of innovative genetic tools, increased funding in research and development, and improved patient outcomes. We offer the following comments and data to support the critical importance of upholding these legal decisions to further foster innovation in the life sciences in the United States.

Response to questions 1, 2, and 3 of the Federal Register notice on the impact of patent eligibility jurisprudence on the conduct of business, investment, and innovation.

The golden age of precision medicine and diagnostics has arisen in no small part due to the current patent eligibility jurisprudence articulated in three unanimous Supreme Court decisions: *Association for Molecular Pathology v. Myriad Genetics, Inc., Alice v. CLS Bank International,* and *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* Previously, people could and did patent not just genes, but also each mutation or variation they detected along with its perceived significance for a patient's health status. Absent current patent eligibility jurisprudence, multiple parties could hold patents relevant to the interpretation of a patient's genomic health even with respect to a single gene and therefore reading and interpreting a patient's full genome would be impeded by an impenetrable "patent thicket." This barrier to the conduct of genomic testing not only harms individual patients who are denied knowledge and understanding of their own health status, it also hobbles the progress of precision medicine which relies upon the conduct and analysis of genomic testing for large numbers of patients to generate new knowledge. Patient care has improved and innovation in genetics has thrived because of the lack of patents on DNA, not in spite of it. With the patent thicket locking up the human genome now cleared, a vibrant industry has sprung up that has led to better patient care, reduced costs to the healthcare system, and increased jobs and revenue for communities.

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 genetic sequencing for which the current patent eligibility jurisprudence has provided freedom to operate. Just five years after the 2013 *Myriad* decision, in 2018, Illumina reached $3.3 billion in revenue while sustaining a gross margin of about 70%.

© 2021 Invitae Corporation. All Rights Reserved.

Illumina – Key statistics

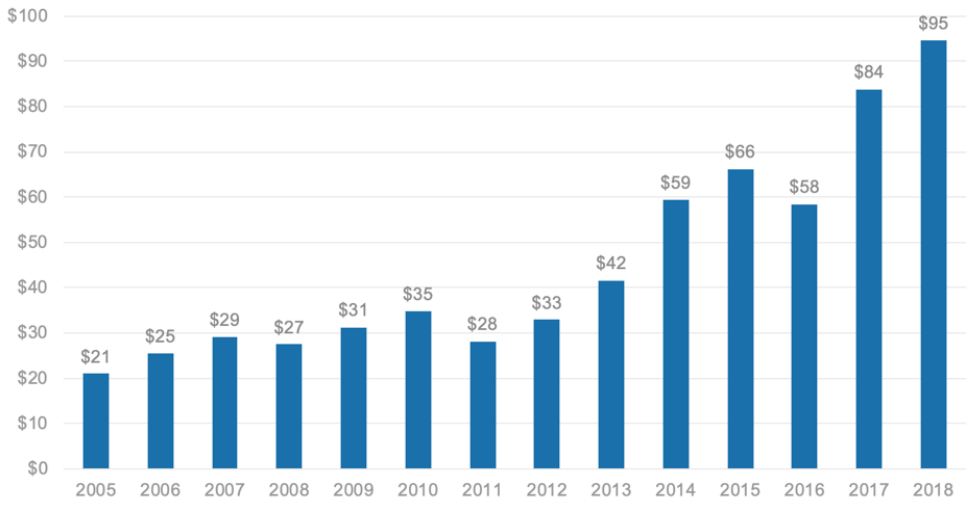
$mm, except per share data	2014	2015	2016	2017	2018
Net Sales or Revenues	1,861.4	2,219.8	2,398.4	2,752.0	3,333.0
Growth	30.97%	19.25%	8.05%	14.74%	21.11%
Cost of Goods Sold	451.1	544.1	591.0	752.0	854.0
% of Sales	24.23%	24.51%	24.64%	27.33%	25.62%
Gross Profit	1,297.7	1,549.3	1,666.4	1,844.0	2,300.0
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.

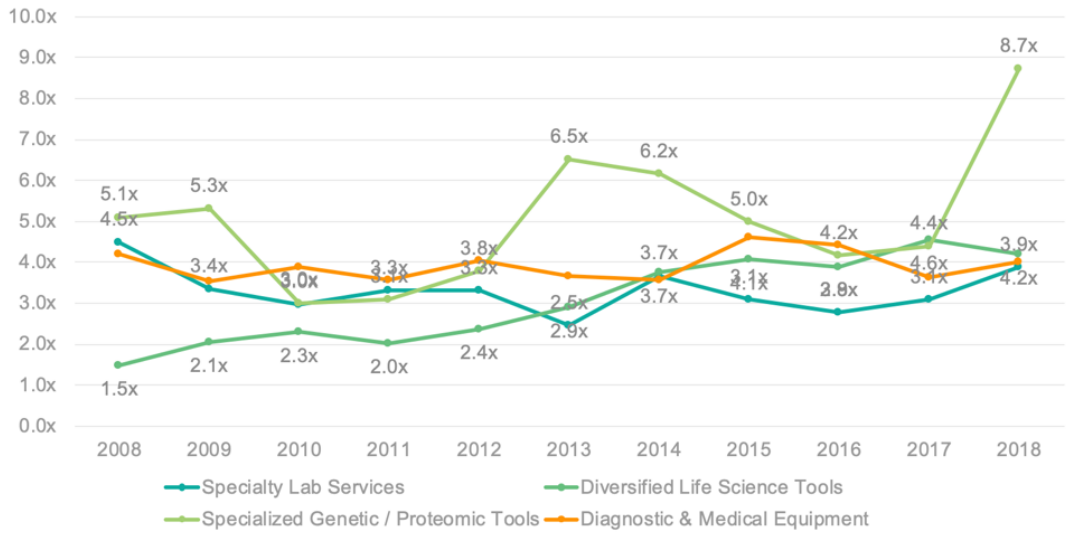
Precision Medicine cumulative market cap ($bn)



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

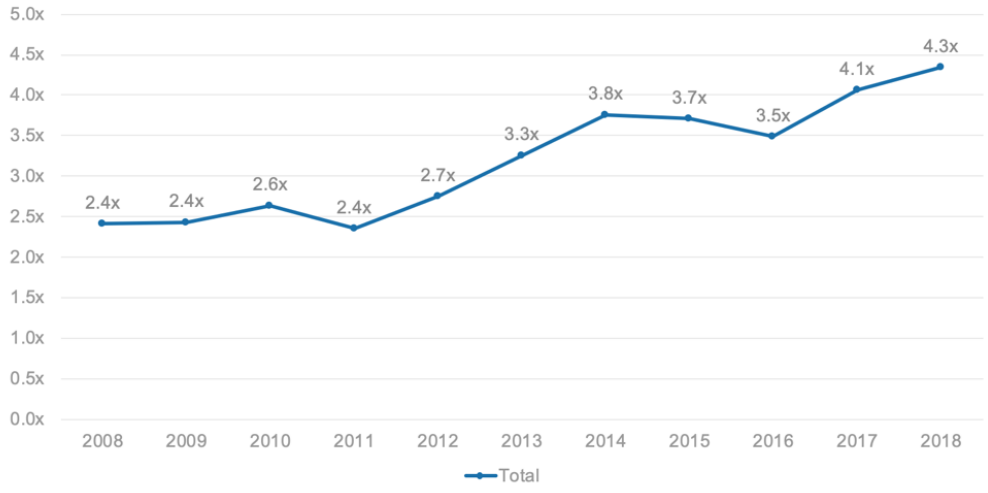
© 2021 Invitae Corporation. All Rights Reserved.

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

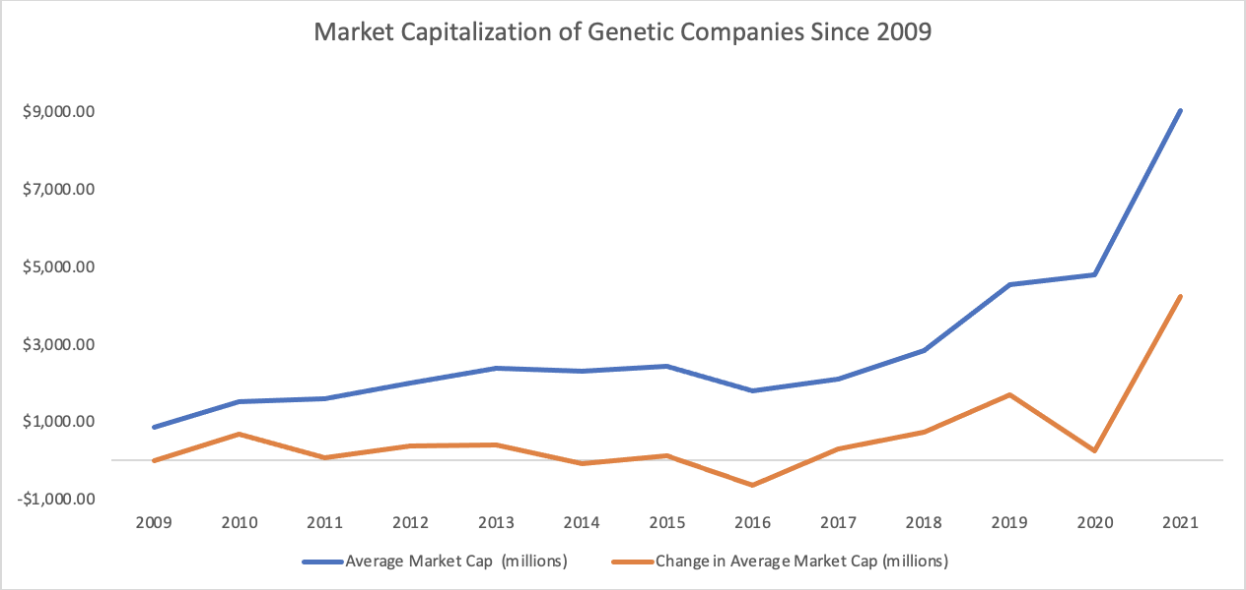
Life Science Tools / Dx revenue multiples (2/2)



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

© 2021 Invitae Corporation. All Rights Reserved.

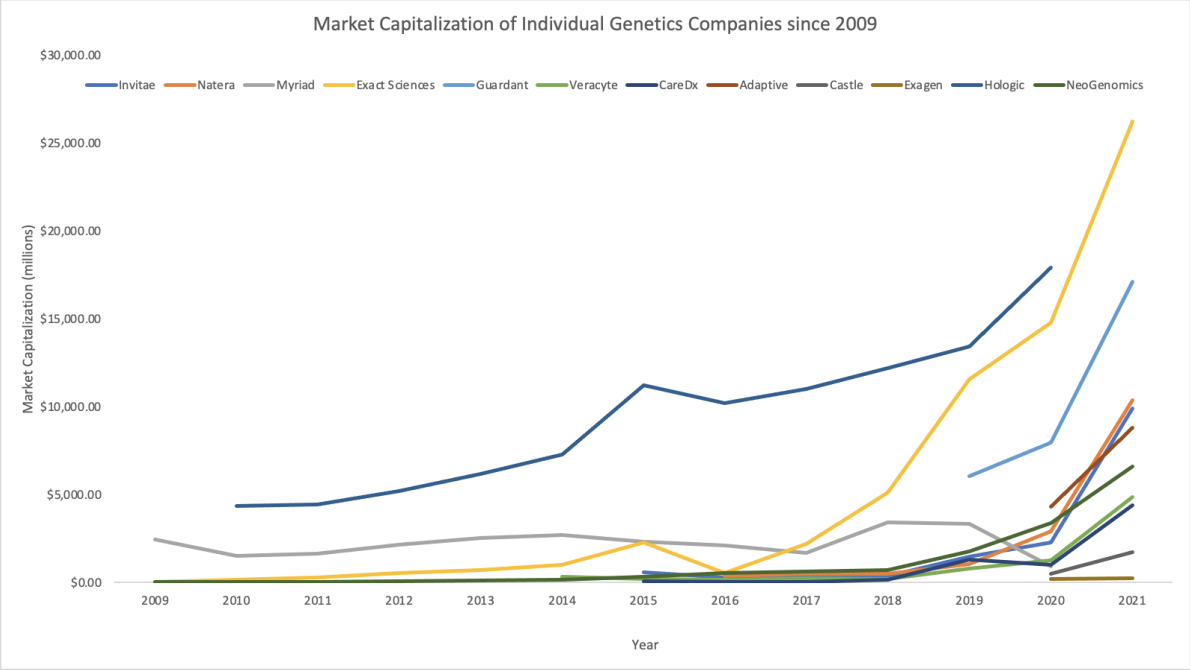
By examining and aggregating data from the 10-K filings and NASDAQ valuations of twelve publicly traded genetic testing companies,[1] we found that market capitalization has increased since the *Myriad* and *Mayo* decisions, indicating that they did not have a negative impact on growth in this sector.



Looking at the data from individual companies, one can see the dramatic growth in these innovative companies. An interesting observation is that Myriad Genetics, Inc., which once owned the patents on the hereditary breast and ovarian cancer genes and their interpretation, saw no major change in their market capitalization from the period before the Supreme Court decision ushering in the current patent eligibility jurisprudence and after 2015 when Myriad abandoned enforcement of such patents directed to patent ineligible subject matter. The loss of those patents had at most a marginal effect on Myriad's market capitalization.

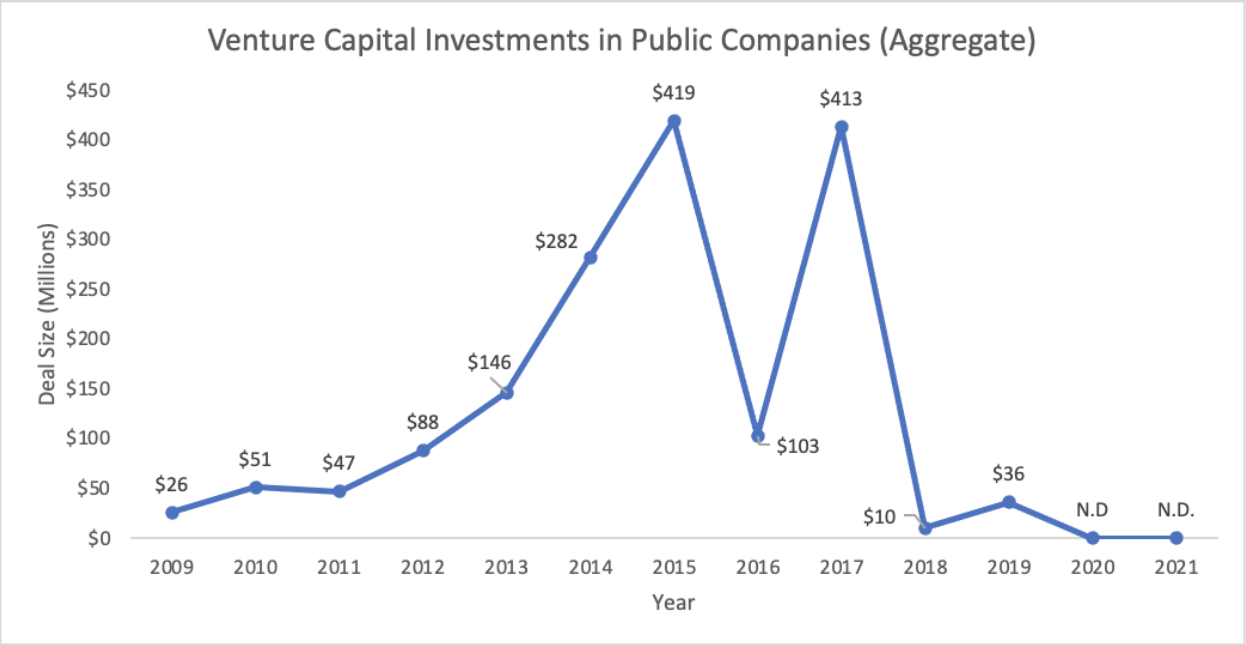
[1] Companies included in the analysis (parentheticals indicate years for which data is provided for each company): Adaptive Biotechnologies Corporation (2020-2021), CareDx, Inc. (2015-2021), Castle Biosciences, Inc. (2020-2021), Exact Sciences Corporation (2009-2021), Exagen, Inc. (2020-2021), Guardant Health, Inc. (2019-2021), Hologic, Inc. (2012-2020), Invitae Corporation (2015-2021), Myriad Genetics, Inc. (2009-2020), Natera, Inc. (2016-2021), NeoGenomics Laboratories, Inc. (2009-2021), Veracyte, Inc. (2014-2021)

© 2021 Invitae Corporation. All Rights Reserved.

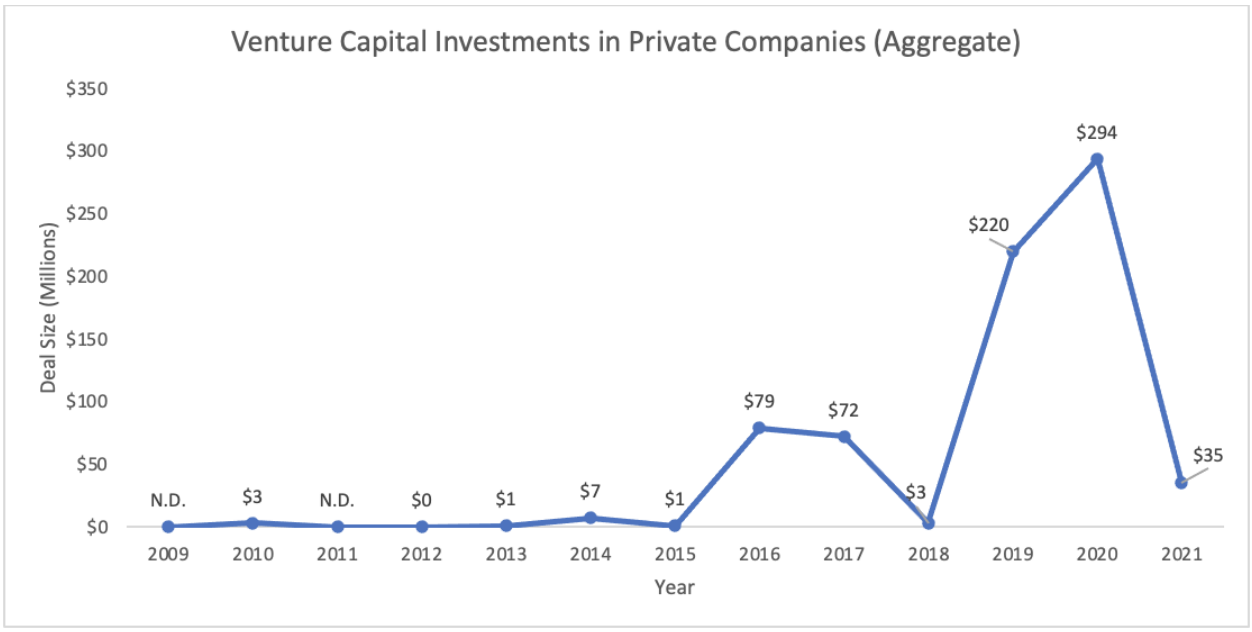


Invitae's CEO, Dr. Sean George, testified before the Senate Judiciary Committee's Subcommittee on Intellectual Property on the State of Patent Eligibility in America in June 2019. In his written testimony, he shared that in 2012, Invitae was turned down by hundreds of investors who said its goal to offer a comprehensive menu of the world's medical genetic tests at lower prices would never work for one reason: the DNA patent thicket. Since the *Myriad* decision in 2013 eliminated that barrier, venture capital funding in genetic testing companies has ballooned. Examining the venture capital investments in companies prior to their initial public offering, the funding more than tripled three years later to a peak in 2015 at $419 million. These companies are widely respected and considered industry leaders in genomic testing: Adaptive Biotechnologies Corporation (2020-2021), CareDx, Inc. (2015-2021), Castle Biosciences, Inc. (2020-2021), Exact Sciences Corporation (2009-2021), Exagen, Inc. (2020-2021), Guardant Health, Inc. (2019-2021), Hologic, Inc. (2012-2020), Invitae Corporation (2015-2021), Myriad Genetics, Inc. (2009-2020), Natera, Inc. (2016-2021), NeoGenomics Laboratories, Inc. (2009-2021), Veracyte, Inc. (2014-2021). (Note: parentheticals indicate years for which data is provided for each company; "N.D." means no data from any company for that year).

© 2021 Invitae Corporation. All Rights Reserved.



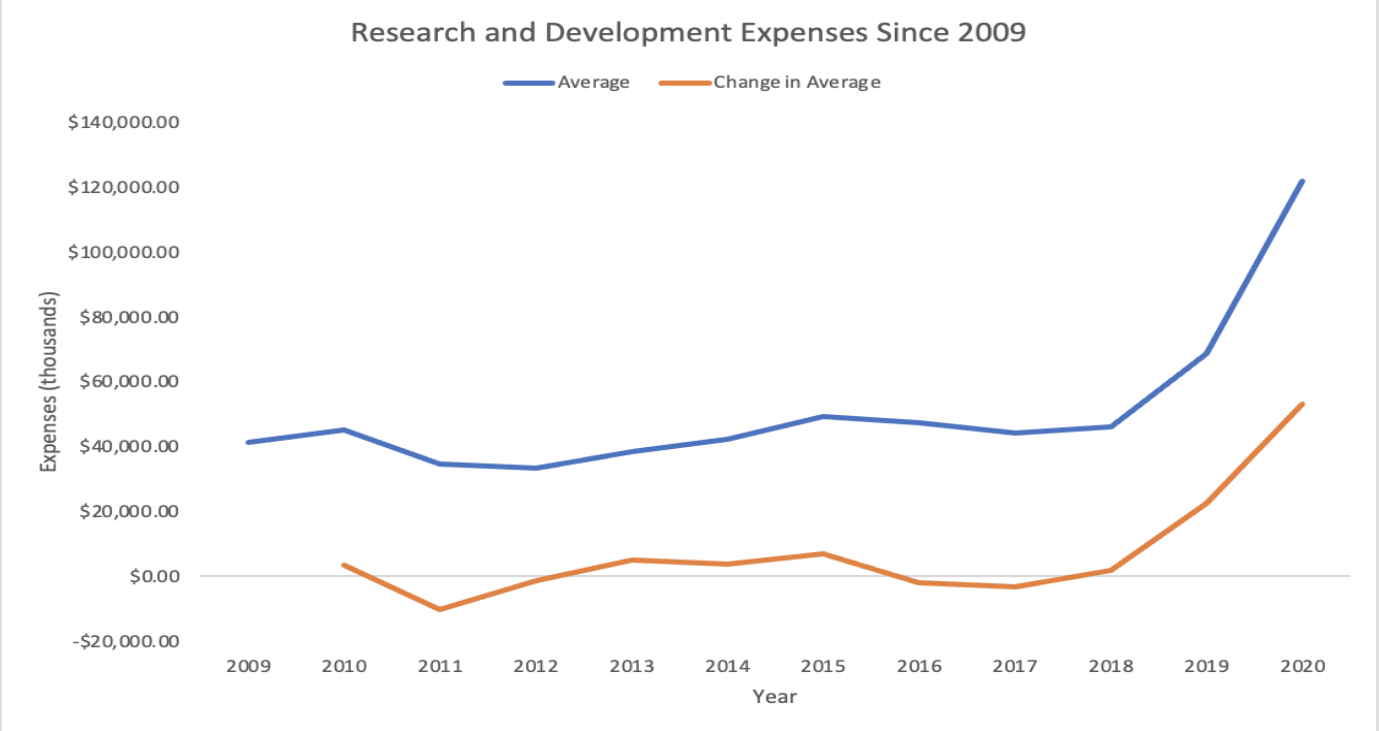
In the years after the Supreme Court's decisions giving rise to the current patent eligibility jurisprudence, venture capital funding for private genetic testing companies showed similar growth. As shown below, aggregate data for BioTheranostics, Inc., Caris Life Sciences, Cernostics, Freenome, and Inivata, Inc. experienced almost a 300 fold increase.



© 2021 Invitae Corporation. All Rights Reserved.

Response to Question 6 regarding research and development activities within the United States:

The Request for Information also inquired about shifting investment in research and development to jurisdictions outside the United States. Invitae has not experienced any need to shift its investment, research and development activities, nor need to move jobs from the United States to other jurisdictions. In fact, we've experienced the opposite and since 2013, we have grown from less than 100 employees to a company with almost 3000 employees and annual research and development expenditures of $240.6 million in 2020. When we examined data on research and development in the US-based diagnostics industry, we found that investment increased in the years following the Supreme Court decisions on patent eligibility. Specifically, as noted in the 10-K filings from the twelve publicly traded genetic testing companies discussed above, spending in research and development has dramatically increased since 2018.



(Note: not all 12 companies contributed data throughout the whole measurement period and some data points may represent the average of fewer than 12 companies.)

Prior to the emergence of the current patent eligibility jurisprudence, the Human Genome Project with a $3 billion budget was one of the largest federal investments in research. A private entity, Celera Genomics (Celera), competed with that public effort, and Celera's efforts ended in

© 2021 Invitae Corporation. All Rights Reserved.

2001 when they published a partial sequence of the human genome[2], and subsequently, they were able to claim patent rights in the genes that had not been sequenced by the public effort. In a 2013 report on the of impact of Celera's intellectual property on subsequent innovation, the author noted that these protections allowed Celera to control licensing for using and commercializing innovations involving those genes which allowed the author to compare the levels of subsequent research and development between Celera's protected genes and those genes able to be freely studied as a result of their publication as part of the Human Genome Project.[3] Making use of this unique natural experiment, the author found that Celera's intellectual protections resulted in a 20 to 30 percent decrease in scientific research and product development. Therefore, having patents on the human genome actually discouraged researchers and hindered these activities.

Question 7 regarding whether the state of patent eligibility jurisprudence led to changes in business strategy.

Invitae has not had to alter its business strategy in light of current patent eligibility jurisprudence to protect its intellectual property. Indeed, Invitae's business strategy, along with that of the entire genetic testing industry, has been enabled by current patent eligibility jurisprudence.

Question 8 regarding changes in behavior with regard to filing, purchasing, licensing, selling, or maintaining patent applications and patents in the US.

Invitae has not altered its behavior in any respect with regard to filing, purchasing, licensing, selling, or maintaining patent applications and patents in the US. We agree that, outside of biomarkers, their association with health status and abstract processes, a wide range of patent-eligible subject matter exists in the precision medicine and molecular diagnostic fields. Specifically, Invitae maintains a significant patent portfolio with claims directed to innovative laboratory techniques, device manufacturing, automation, and other technologies that confer commercial advantage and enable Invitae to offer higher quality services to more patients at more affordable prices. Invitae also recognizes the patent rights of others by obtaining licenses to practice the patented technology of others, where appropriate.

[2] 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

[3] Williams, H. Intellectual Property Rights and Innovation: Evidence from the Human Genome. Journal of Political Economy. 2013;121(1):1–27. https://www.journals.uchicago.edu/doi/pdf/10.1086/669706

© 2021 Invitae Corporation. All Rights Reserved.

Question 13 regarding availability, effectiveness, or cost of personalized medicine and diagnostic inventions.

Since 2013, access to and the availability of genetic testing has increased dramatically. The day before the *Myriad* decision in 2013, only one laboratory offered testing for hereditary breast and ovarian cancer and the day after the decision, at least five companies began offering testing for this indication.[4] Today, according to the Genetic Test Registry housed at the National Institutes of Health, there are 466 clinical tests available for the *BRCA* genes.[5] In 2018, Concert Genetics tallied the clinically available genetic tests at approximately 75,000 with 14 new tests introduced daily.[6] In 2020, the tally is now more than 160,000 clinically orderable genetic tests on the market.[7] Since the barrier of patents on DNA has been removed, patients and their providers have vast choice in selecting appropriate clinical testing.

Additionally, the *Myriad* decision resulted in a reduction in the cost of genetic testing for both private and public payers as well as improvements in the quality of the tests. We offer three historical examples that illustrate how patents discourage development of clinical testing with potentially deadly consequences for patients and their families.

Within hereditary breast cancer alone:

- The cost of testing plummeted from $4,400 in 2013 to a $250 cost to the patient at Invitae today.
- The turnaround time for results fell from months to days, which is essential for healthcare providers and patients to plan and make time-sensitive decisions about life-altering surgery, such as a risk-reducing mastectomy to reduce the risk of developing hereditary breast cancer.
- 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 an entire patent thicket across scores of genes were required.
- Research is constantly ongoing in the field of hereditary cancer. Patenting a gene will severely limit the ability to include newly discovered genes that are associated with an increased risk of cancer from being included in a panel. This will have an adverse impact on patient outcomes if panel tests cannot be updated with the most current research.

[4] https://www.nytimes.com/2013/06/14/business/after-dna-patent-ruling-availability-of-genetic-tests-could-broaden.html
[5] https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=672[geneid]&filter=testtype:clinical
[6] http://www.concertgenetics.com/wp-content/uploads/2018/04/12_ConcertGenetics_CurrentLandscapeOfGeneticTesting2018.pdf
[7] https://www.concertgenetics.com/resources/concert-genetic-testing-unit-gtu/

© 2021 Invitae Corporation. All Rights Reserved.

It has been known since 1999 that large rearrangements in *BRCA1* are likely responsible for approximately 10% of all disease-causing mutations in hereditary breast and ovarian cancer.[8] Yet, the company that held exclusive testing rights under their patent originally used a testing approach (short-range polymerase chain reaction followed by genomic sequencing) that only accounted for the five most common types of rearrangements in the *BRCA1* and *BRCA2* genes. Thus, the test that launched in 2002 potentially missed 12% of genomic rearrangements that can be detected using other technology.[9] It took another four years for a test able to detect all known large rearrangements to be made available, and it has been speculated that this was only in response to significant pressure from the scientific community to improve the methodological approaches in clinically offered tests.[10] 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.

Patents also greatly hindered the development of testing for familial long QT syndrome, an inherited heart rhythm disorder that can lead to sudden cardiac death. 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[11] 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.[12] 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. The lack of patient access to this test due to the patents likely contributed to a number of preventable deaths from sudden cardiac arrest. 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.[13] 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.

---

[8] 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.

[9] 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

[10] 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.

[11] 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

[12] 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.

[13] 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.

© 2021 Invitae Corporation. All Rights Reserved.

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 (US 5922855 and US 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, enabling patient access to testing panels currently recommended by all professional clinical guidelines.[14] 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 breast cancer, at least nine laboratories were offering testing for Lynch syndrome allowing laboratories to compete by making improvements to quality, turnaround time, convenience, and cost, and providing patients a choice in testing.

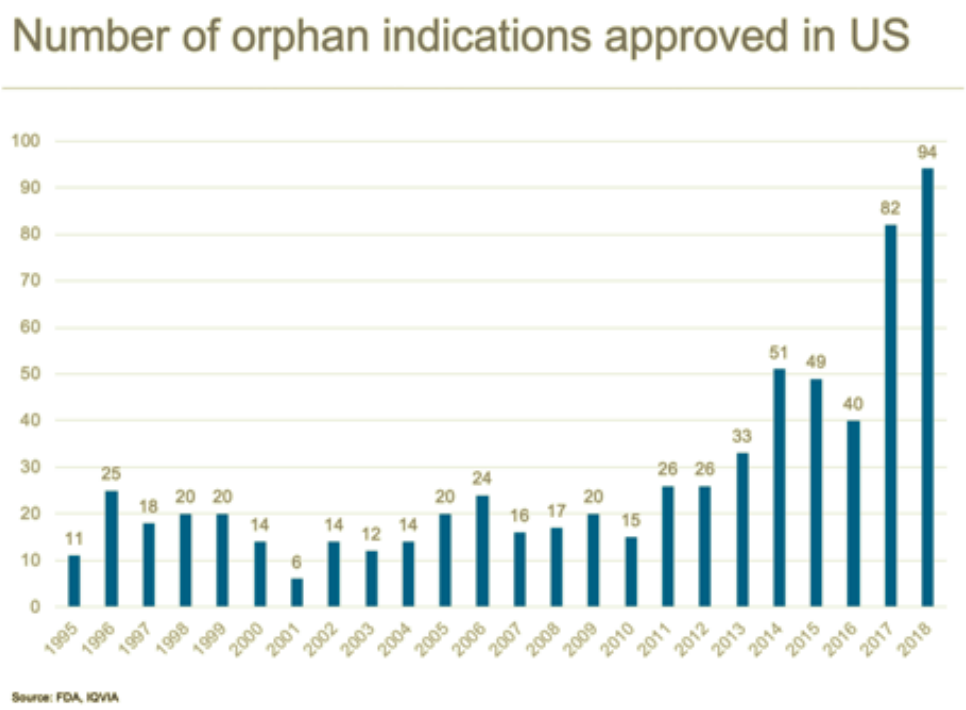
Now that the Supreme Court decisions have helped to make a genetic diagnosis more affordable and accessible, we've also seen a corresponding boom in precision therapeutics with the availability of gene-linked therapies at an all-time high. They are bringing hope to patients battling diseases like cystic 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[15] and in 2018 when drug approvals reached an all-time high, orphan drugs for rare, often genetic, disorders accounted for more than half of all approvals.[16] The broad availability and low-cost of genetic sequencing is a core driver of this success because genetic screening is so often necessary to identify the patient population receptive to such drugs.

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

[15] 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

[16] 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

© 2021 Invitae Corporation. All Rights Reserved.



It is clear that after the Supreme Court decisions giving rise to the current patent eligibility jurisprudence, investment and innovation in diagnostics and precision medicine has increased dramatically. The benefit of these advancements lies not just in maintaining American leadership in the field, but also in the improved standard of care allowing many more patients to obtain an earlier diagnosis, prevent disease altogether, or receive a tailored more effective treatment. We hope that after reviewing the data presented that you will recognize that the current patent eligibility jurisprudence has greatly benefited and accelerated both clinical availability and continuing innovation in precision medicine which is rooted in an evolving understanding of the human genome and other biomarkers.

Thank you again for the opportunity to provide our comments and this data for your consideration. We hope that it informs your study and successfully demonstrates that patent eligibility jurisprudence has resulted in unprecedented innovation in precision medicine and diagnostics for industry and has provided remarkable improvements in health outcomes and improved access to these innovative tools for patients and their families. Given the significant investments, growth, and size of the genetic testing industry today, we do not believe that a

© 2021 Invitae Corporation. All Rights Reserved.

policy change is warranted. Invitae agrees with the Supreme Court decisions that biomarkers, including DNA, and their associations with health status are natural phenomena and natural laws and therefore should not be patent eligible. If we may be of further assistance, please contact me at lee.bendekgey@invitae.com.

Sincerely,

Lee Bendekgey
Chief Policy Officer
Invitae Corporation

© 2021 Invitae Corporation. All Rights Reserved.