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Commercial Landscape of noninvasive prenatal testing in the United States

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Abstract

Cell-free fetal DNA-based noninvasive prenatal testing (NIPT) could significantly change the paradigm of prenatal testing and screening. Intellectual property (IP) and commercialization promise to be important components of the emerging debate about clinical implementation of these technologies. We have assembled information about types of testing, prices, turnaround times and reimbursement of recently launched commercial tests in the United States from the trade press, news articles, and scientific, legal, and business publications. We also describe the patenting and licensing landscape of technologies underlying these tests and ongoing patent litigation in the United States. Finally, we discuss how IP issues may affect clinical translation of NIPT and their potential implications for stakeholders. Fetal medicine professionals (clinicians and researchers), genetic counselors, insurers, regulators, test developers and patients may be able to use this information to make informed decisions about clinical implementation of current and emerging noninvasive prenatal tests.

Introduction

Non-invasive prenatal testing (NIPT) using cell-free fetal (cff) DNA circulating in maternal blood may allow for earlier detection of genetic diseases and aid in reproductive decision-making and pregnancy management¹. The clinical introduction of this testing raises several ethical and practical challenges.^{2–5} Several applications of NIPT (RhD blood type and paternity testing) are already in use, and testing for common chromosomal aneuploidies such as trisomies 13, 18, and 21 became commercially available in 2011. Compared to prenatal screening or diagnostic tests that are currently standard of practice, the clinical translation of NIPT technologies has been predominantly spearheaded by industry. As technologies for non-invasively analyzing the fetal genome advance, the commercial landscape of NIPT will likely continue to evolve, expand, and raise novel implementation issues.

The prenatal testing market, estimated to be worth up to 1.3 billion USD a year,⁶ is seen as an extremely lucrative segment of active growth for the diagnostics industry. Foundational technologies for isolation and genetic analysis of cffDNA have been patented or exclusively licensed to a small number of companies in the US and internationally.⁷ Indeed, companies and academic institutions continue to actively seek patents worldwide for technologies

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related to NIPT, and patents rights surrounding NIPT are being extensively litigated in the United States.

Patenting could have both positive and negative effects on the availability of tests, clinical adoption, and patient access to NIPT. Perceived or real IP barriers could reduce market competition, limit quality assurance and improvement mechanisms, decrease availability of alternative or cheaper tests, and reduce the cost effectiveness of NIPT. Alternatively, companies with dominant IP positions may be more motivated to secure broad insurance coverage for their tests and invest in expensive research and development and regulatory approval processes, particularly if these tests are regulated as biomedical devices or kits. How patents will influence clinical implementation of NIPT remains to be seen but is an area of increasing concern.^{7, 8}

The commercial and IP landscape of NIPT is quickly changing, even as the first generation of tests is being introduced. Information about costs, reimbursement, patenting and licensing of commercial tests is being published in trade press, news media and business publications, but may not be readily accessible to clinicians and health care providers. The objective of this review is to bring together such information from scientific, legal, news and business publications and to discuss its implications. While developments in NIPT technology and commercialization are occurring worldwide, this review will focus primarily on the US, where IP issues have been especially pronounced and where several commercially developed tests have rapidly entered the market and clinics just within the last two years. Discussion will also be limited to NIPT that makes use of cffDNA, although the use of fetal cells, proteins, or RNA circulating in maternal blood for prenatal diagnostics is also being actively explored.

This information may help health-care providers and health systems evaluate these new tests and make informed decisions about incorporating NIPT in clinical practice. These discussions may also allow stakeholders to develop a deeper understanding of the harms and benefits of patenting, licensing and commercialization strategies.

Commercial Landscape of cffDNA-based NIPT

For decades, there has been interest in the commercial development of NIPT, as evidenced by the many patents filed on methods for detecting genetic abnormalities in circulating fetal cells. However, commercial exploration of NIPT was dramatically propelled forward by the discovery of cffDNA, which comprises about 10% of DNA in maternal circulation and becomes detectable five weeks after conception.¹ CffDNA became a promising source of fetal genetic material for NIPT, as it could be accessed early in pregnancy without the risk of harming the fetus unlike invasively-obtained fetal genetic samples. Researchers began looking for ways to utilize cffDNA in maternal plasma for prenatal screening and diagnosis, particularly for detecting common chromosomal aneuploidies. However, the admixture of ostensibly similar maternal and fetal DNA posed significant challenges.⁸ As new technological platforms for genetic analysis and sequencing, such as next-generation massively parallel sequencing (MPS), became available, fetal aneuploidy detection using cffDNA became broadly feasible.

Interest in the development of this technology arose quickly, and many patent applications were filed worldwide for the use of cffDNA in NIPT. As described below and in Table 1, at least four companies have brought noninvasive tests to market within the last 2 years, and others are preparing to launch their tests in the near future. Four US-based companies - Sequenom, Verinata Health (recently acquired by Illumina), Ariosa Diagnostics, and Natera - are marketing laboratory-developed tests that use a combination of PCR and sequencing technologies and proprietary algorithms to analyze cffDNA for chromosomal aneuploidies

(see Table 1). These highly sensitive and specific tests currently detect the most common chromosomal aneuploidies, including trisomies 21 (Down syndrome), 13 (Patau syndrome) and 18 (Edwards syndrome). Some tests are also being used to detect common sex chromosome aneuploidies and fetal sex.

Sequenom was the first to launch its MPS-based test, MaterniT21 (now MaterniT21 Plus) for trisomy 21 in October 2011, and the test was soon expanded to detect trisomy 13, trisomy 18, and sex chromosome aneuploidies.⁹ The MaterniT21Plus test is available beginning at ten weeks gestation and requires a physician to order the test. Sequenom has also been marketing the SensiGene Fetal RhD genotyping test, which uses real-time PCR and mass spectrometry, in the US since 2010.¹⁰ Sequenom's testing laboratory has Clinical Laboratory Improvement Amendments (CLIA) certification and has received accreditation from the College of American Pathologists (CAP). The company now projects an annual run rate of 120,000 tests,¹⁰ and the test is available in several countries.¹² Sequenom reports that out-of-pocket costs for the MaterniT21 Plus test will be \$235 for patients covered by insurance or \$1700 for those without insurance coverage (Table 1).^{10,13} Sequenom has published the results of several studies that demonstrate the performance of its tests, and several clinical trials are ongoing (Table 1).¹³

Verinata Health (Verinata, previously Artemis Health) also uses MPS technology in its Verifi test for detecting trisomies 13, 18, and 21 and sex chromosome aneuploidies.¹⁴ The test is also available at 10 weeks gestation and needs to be ordered by a physician. The test costs \$495 for patients paying out-of-pocket or \$200 co-pay for patients with qualifying insurance.^{15, 16, 97} Verifi is offered within the US, including through PerkinElmer's prenatal testing menu, and testing is conducted at the company's laboratory, which is certified by CLIA and accredited by CAP.¹⁵ Verinata has several ongoing and published clinical trials (Table 1). Illumina acquired Verinata early this year and has indicated it may seek FDA clearance as a device for the Verifi test in the coming years.¹⁷

Ariosa Diagnostics (Ariosa, previously known as Tandem Diagnostics and Aria Diagnostics) was the third company to begin offering NIPT in the US. Its Harmony Prenatal Test uses targeted sequencing of selected chromosomal loci to detect aneuploidies, including trisomies 13, 18, and 21. Test samples may be collected beginning at 10 gestational weeks by the ordering physician or through any Laboratory Corporation of America site in the United States.¹⁸ The Harmony Prenatal Test costs \$95 for patients with insurance coverage or \$795 out-of-pocket for those without qualifying insurance.^{6,18,19} Ariosa's laboratory has received both CLIA certification and CAP accreditation.¹⁸ The company has published results of several ongoing clinical trials in peer-reviewed journals (Table 1).

Finally, Natera (previously Gene Security Network) has developed a targeted sequencing platform incorporating its Parental Support algorithm²⁰ for non-invasive detection of trisomy 13, 18, and 21, and sex chromosome aneuploidies into its Panorama Test.^{20,21} This must be ordered through a physician and is available as early as 9 weeks into pregnancy for \$1495 without insurance coverage.²² The test is conducted through Natera's CLIA-certified and CAP-accredited laboratory.²³ Natera recently announced that the Panorama test will be available nationwide through Quest Diagnostics starting April 2013 and through the GenPath business unit of BioReference Laboratories Inc.^{23,24} The company is also conducting two validation studies for the use of cfDNA to detect microdeletions and microduplications (Table 1). Natera also offers non-invasive prenatal paternity testing using single nucleotide polymorphism (SNP) microarray technology through a licensing agreement with DNA Diagnostics Center.²⁴

Data comparing the performance of these tests directly to each other are not available. All four companies have reported comparable specificity and sensitivity based on clinical studies they have conducted (see Table 1 for citations of published clinical studies.) Sequenom is estimated to have captured about 12 percent of the US high-risk pregnancy market according to one analyst, possibly due to its first mover status.²⁴ It remains to be seen if the market entrance of Verinata, Ariosa and Natera at significantly lower price points, will cut into Sequenom's market share.

At least three additional US-based companies have expressed interest in developing NIPT for chromosomal aneuploidies. Ravgen currently offers NIPT for paternity determination and may offer a prenatal test for single gene disorders, including cystic fibrosis and sickle cell disease, on a limited basis in the United States.²⁵ The paternity test may be available as early as five weeks into pregnancy, and it is unclear whether a physician needs to be involved in ordering the test.²⁶ The cost for the paternity test ranges between \$950 and \$1650.^{25,26} No information on Ravgen's single-gene disorder tests and their costs is currently available. Ravgen's laboratory has received CAP accreditation and CLIA certification, and the company has published at least three peer-reviewed papers detailing methods for cffDNA processing and determination of fetal aneuploidies and paternity.^{27–29}

Cellular Research is seeking to develop a microarray-based test to non-invasively detect trisomy 21 and other chromosomal aneuploidies. The company is utilizing technology developed at Affymetrix and holds rights to at least one relevant patent application.³⁰

TrovaGene may also be developing technologies using MPS to analyze fetal DNA fragments found in maternal urine.³¹ TrovaGene has received CLIA certification and CAP accreditation for its laboratory. It is not clear where in the research, development, and commercialization processes Trovagen stands.

Some United States-based companies may also be offering noninvasive prenatal testing for fetal sex or paternity directly to consumers; the use of these tests is generally outside the realm of the traditional healthcare system. Additionally, other firms in the US may be developing NIPT using fetal cells, proteins, or cffRNA, rather than cffDNA, circulating in maternal blood.

Outside the United States, several commercial and academic laboratories, including Berry Genomics, BGI Health, and The Chinese University of Hong Kong in China; LifeCodexx in Germany; Radboud University Nijmegen in the Netherlands; and NIPD Genetics in Cyprus, are offering or developing cffDNA-based NIPT for fetal aneuploidies and other genetic conditions.^{32–36} Ariosa's test is available in the UK through commercial laboratories.^{18,37,38} In addition, United Arab Emirates-based Newbridge will be offering the Verifi test in the Middle East Africa, Turkey and Cyprus.⁹⁶ Similarly, Sengenics in Kuala Lumpur, Malaysia has entered an exclusive agreement to offer MaterniT21Plus test in Malaysia and Singapore.³⁹

Intellectual Property Landscape of cffDNA-based NIPT

Several companies have received patent protection for their technologies or obtained exclusive rights to key technologies and continue to actively seek more IP protection. At this time, few data are publicly available on patenting and licensing of technologies underlying NIPT. We have therefore assembled a patent landscape for NIPT using data available in patent databases, trade press, peer-reviewed publications and news articles, current through 15 December 2012. We focused on the landscape in the United States primarily because major companies marketing NIPT are United States-based and patents in this country have been issued earlier compared with those filed in Europe and other jurisdictions.

We identified 34 active US patents that contain at least one claim covering uses of cffDNA for prenatal genetic testing (Figure 1). (See Table 2 for additional information.) All the identified patents contain only method claims and no claims on composition of matter such as DNA sequences or fetal nucleic acids. The methods claims cover a range of diagnostic techniques for performing genetic analyses on cff nucleic acids (DNA and RNA) and for detecting fetal sex, RhD status, fetal aneuploidies and mutations in specific genes. Many of these patents have been filed in other countries and Europe. Details about where these patents have been filed or granted can be found in the full text of each patent or application through the United States Patent and Trademark Office (USPTO) website. As shown in Table 3, universities and nonprofit institutions own a majority of these patents. At least 90 US applications related to NIPT using cffDNA are pending (Table 3), and it is likely more have been filed and are not published in the USPTO database yet because they are not 18 months old. Based on our understanding of the technologies, we analyzed patent claims to identify the major US patents and applications that are most likely directly related to currently marketed and expected NIPT technology.

US6258540, awarded to Dennis Lo in 2001, is widely considered to be a foundational patent and may broadly cover most applications for NIPT. The '540 patent is assigned to Isis Innovation Ltd., the commercialization arm of Oxford University, where Dr. Lo initially conducted research on cffDNA. Isis Innovation Ltd. awarded worldwide exclusive rights to this patent to Sequenom in 2005.⁴⁰ Sequenom has stated that exclusive rights to the '540 patent give it a dominant IP position and that all other developers will be required to obtain licenses for use in their tests.⁴¹ In addition, Sequenom has licensed at least two United States patents^{42,43} and three applications from the Chinese University of Hong Kong.⁴⁰ The Chinese University of Hong Kong has retained rights to these patents for research and academic use and for offering noninvasive trisomy testing in Hong Kong.⁴⁴ Sequenom has awarded one sublicense to LifeCodexx for developing and marketing a noninvasive test for trisomy 21 in parts of Europe.⁴⁵ The company has also accumulated significant IP covering sequencing-based methods for NIPT including patents that it purchased recently from Helicos Biosciences.⁴⁶ Sequenom controls the IP underlying cffDNA-based RhD testing in the US.⁴⁷

Verinata Health (now owned by Illumina), has acquired worldwide exclusive rights to at least three US patents: US7888017, US80080182,⁴⁸ and US8296076, each granted to Stanford University (Table 3).⁴⁹ Verinata has also been awarded two United States patents and filed at least nineteen applications related to NIPT (Table 3). Ariosa has obtained rights to US7799531 assigned to the University of Louisville covering methods for determining fetal aneuploidy in a maternal sample using targeted sequencing (Table 3). It is not clear if the University of Louisville has also granted Ariosa rights to other patent applications filed by Aoy Tomita-Mitchell and colleagues (Table 3). Natera has not been awarded any patents to date, but inventors Mathew Rabinowitz and colleagues have filed at least eight applications covering targeted sequencing and algorithms for analysis of cffDNA for aneuploidy detection (Table 3). Ravgen has not enforced its patents in the US but pursued an unsuccessful opposition proceeding before the European Patent Office against Sequenom's European Patent 994963.^{40,50,51} Trovagene had initially licensed its patent US6251638, which covers transrenal DNA analysis technology, to Sequenom in 2008, but recouped these rights in a 2009 lawsuit against Sequenom.^{52,53}

Patent Litigation and NIPT

All four major United States companies – Sequenom, Verinata, Ariosa, and Natera - are currently embattled in lawsuits over enforcement and infringement of patents.²⁰ Three patents have been particularly prominent in recent litigation: Sequenom's US6258540 *Non-*

invasive Prenatal Diagnosis and Verinata's patents US 8008018 *Determination of Fetal Aneuploidies by Massively Parallel DNA Sequencing* and US8296076 *Noninvasive Diagnosis of Fetal Aneuploidy by Sequencing*. In January 2012, Sequenom filed a lawsuit against Ariosa requesting a preliminary injunction against the company to prevent it from introducing the Harmony Prenatal Test.^{2,4} Sequenom also filed suit against Natera, claiming that the company was encouraging other companies to infringe on its patent by licensing its noninvasive paternity test to DNA Diagnostics Center.⁴ In response, Natera, and Ariosa counter-sued Sequenom maintaining that their different testing methods do not infringe upon the '540 patents and that Sequenom was misrepresenting its patent rights to prevent competitors from entering the market. The companies also assert that some of the claims in the '540 patent are invalid.² Additionally, Verinata is suing Sequenom for infringing upon its '018 patent⁵⁴ and recently sued Ariosa for infringing on its '076 patent.⁵⁵

Intellectual Property Rights – Uncertainties and Implications

The current IP landscape for cffDNA-based NIPT is complex. Over 100 patents and applications contain claims covering methods for detecting, isolating and analyzing cffDNA. The effect of these patents and applications on those developing new or alternative tests will depend on the scope of their claims, their validity in light of expected court decisions and the business decisions of the patent holders (e.g., patent enforcement, litigation, sublicensing). In addition to litigation, it appears that companies may also become involved in patent interference proceedings. These are administrative proceedings conducted by the Board of Patent Appeals and Interferences at the USPTO to determine which applicant is entitled to a patent or its specific claims if both companies have claimed the same invention in pending applications or issued patents. The USPTO recently withdrew a patent US 8340916 entitled *Diagnosing Fetal Chromosomal Aneuploidy Using Massively Parallel Genomic Sequencing* issued to The Chinese University of Hong Kong and licensed exclusively to Sequenom due to pending applications with overlapping claims from other institutions.⁵⁶

The outcome of ongoing litigation is difficult to predict, but one potential outcome is that a single company may secure a market monopoly by being granted injunctions against its competitors. On the other hand, if companies are successful in challenging the validity or narrowing the scope of patents through litigation, there may be more freedom to operate or more opportunity for cross-licensing patents between companies.

Concerns about diagnostic monopolies include that they will result in higher test costs, lower test availability and quality, fewer testing options for patients, and hampered test innovation and clinical research,^{57,58} thus reducing the quality of clinical care and decreasing patient access.⁵⁹ Such concerns may be more pronounced in the United States, as all cffDNA-based NIPT is available only from commercial laboratories rather than academic medical center or hospital-based laboratories. Previous empirical research suggests that patenting and licensing practices, specifically exclusive licensing, have at least transiently reduced availability of genetic testing for several diseases such as long QT syndrome and hereditary breast and ovarian cancer.^{60–63} Surveys of genetic testing laboratories showed a reduction in the number of providers offering patented genetic tests in the United States.⁶⁴ Access to genetic testing was the subject of a more recent study by the Secretary's Advisory Committee on Genetics, Health and Society's Task Force on Patents and Licensing.^{65,66} Although this study found little evidence that patents substantially or pervasively either helped or hindered patient access to genetic testing in the United States, it was clear that problems do arise when patents covering genetic tests are licensed exclusively to a single test provider. When that sole provider does not offer all forms of genetic testing or does not have coverage and reimbursement agreements with insurers or specific health plans, some

patients have no alternative for testing. To the extent that a sole provider may not have incentives to adopt optimal testing methodologies or reduce test prices even if underlying technologies become cheaper, patents and exclusive rights could also reduce cost effectiveness for health systems.^{67,68}

If a monopoly emerges, patient access to NIPT may be limited especially if the sole provider does not have agreements with specific third party payers or health plans (e.g. state Medicaid programs that may cover up to 60% of births in some states).⁶ Currently, all four companies with aneuploidy tests on the market appear to have secured some insurance coverage although no company has disclosed a complete list of third-party payers. Reimbursement rates and out-of-pocket costs may differ depending on the insurer and the individual plan. It also remains to be seen how widely these tests will be covered by Medicaid and state-based health programs. For example, according to one report, Ariosa's test is covered by California's Medicaid program while Verinata and Sequenom's tests are not.⁶ Interestingly, it appears that in other states, women enrolled in Medicaid can get Sequenom's test free of cost.⁶⁹ Natera has indicated that Medicaid and Tricare patients will pay no upfront fees and those without insurance may qualify for financial assistance through the *Natera Cares* program.²⁴ Similarly, other companies may offer similar patient assistance programs to cover out-of-pocket expenses.⁹⁷

On 5 July 2012, the U.S. District Court for the Northern District of California denied Sequenom's request for a preliminary injunction against Ariosa.⁹⁹ In the court's decision Judge Susan Illston noted:

'However, the direct result of a preliminary injunction would be to put Ariosa – whose single product is the Harmony Test – out of business. This would also remove a significantly more efficient, less expensive, and allegedly more accurate test from the market and restrict the access to the noninvasive prenatal nucleic acid tests to only high-risk women.¹⁹ As such both the balance of hardships and the public interest likewise weigh against granting a preliminary injunction.'

Sequenom has stated it will continue litigation against Ariosa.¹⁰⁰ The outcomes of the other lawsuits among these four companies are awaited. However, this recent decision suggests courts are cognizant of the potential effects on patient access due to a market monopoly.

Even in the absence of market monopolies, IP-related issues (e.g. royalty fees, costs of inventing around patents, financial effects of expensive legal proceedings) could affect how tests are priced. A recent study analyzing women's perceptions about barriers to access to prenatal care services identified out-of-pocket costs of services as key factors contributing to "clinic or provider" related barriers.¹⁰¹ Depending on how tests are priced and reimbursed, those who are not covered or who cannot afford the out-of-pocket costs may not be able to receive these new tests. This raises concerns that women from low-income families may be disproportionately impeded in using noninvasive tests, exacerbating the disparity in access to prenatal care.^{71–73}

Companies are also continuing to acquire IP rights for technologies related to NIPT applications that are yet to enter the market, such as noninvasive tests for single gene disorders. Moving forward, test developers may also encounter patents covering human gene sequences or mutations that will be interpreted in these tests, as well as patents on diagnostic methods, platform technologies and diagnostic algorithms. NIPT developers could thus face difficulties aggregating rights to many patent claims or securing rights already exclusively licensed to others by prior agreement, which could result in increased test prices or delayed development of clinically beneficial tests.⁷⁴ It remains to be seen, however, how effectively

companies will be able to exert their patent rights against emerging tests, which will depend to some degree on the outcome of ongoing litigation and cases to come.

Commercialization of NIPT – Implications for Stakeholders

Companies developing NIPT are operating in a highly competitive and litigious environment. Some are quickly expanding their test menus to differentiate themselves and capture market share. Health providers, researchers, and patient advocates should critically monitor commercial offerings of NIPT for changes that may impact clinical practice or raise social or ethical concerns. Professional societies such as the American Congress of Obstetricians and Gynecologists and the National Society of Genetic Counselors should continue to expediently develop guidelines and set standards of laboratory practice and clinical care as NIPT applications continue to evolve.^{75,76} Otherwise companies, operating primarily under market pressures may set *de facto* standards of practice and shape the clinical implementation of NIPT under these pressures alone. Comparing currently available tests with each other, with standard of care technologies and with emerging technologies is particularly important for appropriate clinical implementation. Funding agencies should hence support clinical studies that can independently assess the clinical validity, utility and cost-benefit or cost effectiveness of new NIPT applications. A large portion of the research underlying currently marketed tests was conducted in academic and nonprofit institutions with funding from government or philanthropic sources.⁷ Funding agencies should hence pay close attention to business models and IP management behaviors of institutions commercializing NIPT, especially because restrictive licensing of government and nonprofit-funded inventions could impact patient access, test innovation, and quality of clinical care.

Companies will likely be gathering valuable data in their commercial testing laboratories about the performance of their tests in various clinical contexts such as in cases of twin pregnancies or mosaicism. They may choose to keep these data proprietary and use them to improve their products or gain a competitive advantage. Yet sharing these data with the clinical and academic communities may help to improve clinical implementation of NIPT. Moving forward, companies could also facilitate technology development and clinical translation by being more transparent about which IP rights are associated with their products and which patents are available for licensing. These behaviors may require creating the appropriate incentive structure for companies including regulatory or reimbursement policies for NIPT that mandate such disclosure. It however remains to be seen if, and how, the United States FDA will regulate noninvasive prenatal genetic testing. Currently all prenatal genetic tests in the US are offered as laboratory developed tests and so far the FDA has chosen not to regulate them.

Conclusion

Clinical integration of noninvasive prenatal genetic tests challenges the current paradigm for prenatal genetic testing.⁶⁹ Indeed, many questions about implementation of NIPT have been raised, and the questions may become more pronounced as NIPT expands beyond detection of chromosomal aneuploidies to potentially include testing for single gene disorders, sub-chromosomal deletions and duplications, or the complete fetal genome.^{77,78} It is important to develop a nuanced understanding of the potential harms and benefits of IP, which is grounded in stakeholders' perspectives and the current regulatory and legal environment. Understanding IP and commercialization-related barriers to clinical adoption and patient access early in the translation pathway can guide policies to ensure efficient implementation of NIPT and appropriate access by all patient populations.

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What is already known about this topic?

- Data about technologies underlying cell-free fetal DNA-based noninvasive prenatal tests and their clinical validity are available in scientific publications. Several papers have detailed ethical and practical concerns surrounding noninvasive prenatal testing.
- Information about the costs, reimbursement and intellectual property associated with recently launched tests are available but not readily accessible to stakeholders.
- There has been limited discussion of issues surrounding patenting and commercialization and their effects on clinical translation of noninvasive prenatal testing.

What does this study add?

- We detail the intellectual property and business landscape of current and emerging noninvasive prenatal tests by bringing together information from trade press, news, legal business and scientific publications.
- We also discuss potential effects of patenting and commercialization on the clinical implementation of noninvasive prenatal testing and patient access.

Figure 1. Patent landscape of cfDNA-based noninvasive prenatal testing in the United States

We first searched for United States patents and applications that contained at least one claim relevant to NIPT. For example, we constructed search algorithms that searched the United States Patent and Trademark Office (USPTO) database for all patents that contained the key words "*noninvasive OR non-invasive AND (prenatal OR fetal)*" in their claims.

Additionally, we performed searches using the names of inventors (e.g. Dennis Lo, Stephen Quake) or the names of various institutions and companies (e.g. Sequenom, Stanford University), chosen from the scientific literature, trade press, and news articles, to identify patents and applications related to NIPT. We next read all the claims of issued patents and included only those patents with at least one claim directly covering uses of cfDNA obtained from a maternal sample (blood or urine) for genetic testing. All patent searches were performed in the Delphion database. Patent data are current as of 15 December 2012. Additional information about these patents is available in Table 2

Table 1

Commercial landscape of noninvasive prenatal testing for fetal aneuploidy in the United States

	Sequenom	Verinata Health	Ariosa Diagnostics	Natera
Test name	MaterniT21 Plus ¹³	Verifi ¹⁵	Harmony Prenatal Test ¹⁸	Panorama Prenatal Test ²⁴
Platform	SEQuireDx technology incorporating massively parallel shotgun sequencing ¹³	Massively parallel sequencing using SAFer algorithm ¹⁵	DANSR technology incorporating targeted sequencing and FORTE algorithm ^{79,80}	Next-generation SNP-based Targeted Aneuploidy Testing ²⁴
Conditions	Trisomy 13, trisomy 18, trisomy 21, and sex chromosome aneuploidies ¹³	Trisomy 13, trisomy 18, trisomy 21, sex chromosome aneuploidies, and fetal sex ¹⁵	Trisomy 13, trisomy 18, and trisomy 21 ¹⁸	Trisomy 13, trisomy 18, trisomy 21, and sex chromosome aneuploidies ^{24,81,82}
Cost	\$1700 out-of-pocket, \$235 co-pay with insurance coverage, and \$2900 directly billed to insurers ^{83,84}	\$295 out-of-pocket, \$200 co-pay with insurance coverage, and \$1200 directly billed to insurers ^{16,97}	\$795 out-of-pocket and \$95 co-pay with insurance coverage ^{18–20,84}	Unknown out-of-pocket and \$1495 directly billed to insurers ²⁴
Turnaround	8 to 10 days ¹⁰	8 to 10 days ¹⁵	8 to 10 days ¹⁸	15days ²⁴
Market entry	October 2011 ⁸³	March 2012 ¹⁵	May 2012 ⁶	December 2012 ²⁴
Marketing	Through physicians ¹³	Through physicians ¹⁵	Through physicians ¹⁸	Through physicians ²⁴
Regulatory status	CAP accredited, CLIA certified, plans to submit an IVD PMA application ^{13,85,86}	CAP accredited, CLIA certified, plans to submit an IVD PMA application ¹⁵	CAP accredited, CLIA certified ¹⁸	CAP accredited, CLIA certified ⁸²
Primary publications	Ehrich <i>et al.</i> ⁸⁷ , Bombard <i>et al.</i> ⁸⁸ , Palomaki <i>et al.</i> ⁸⁹ , Palomaki <i>et al.</i> ⁹⁰	Sehnert <i>et al.</i> ⁹¹ , Bianchi <i>et al.</i> ⁹⁸	Sparks <i>et al.</i> ⁷⁹ , Sparks <i>et al.</i> ⁸⁰ , Ashoor <i>et al.</i> ⁹² , Norton <i>et al.</i> ⁹³ , Ashoor <i>et al.</i> ⁹⁴ , Nicolaides <i>et al.</i> ⁹⁵	Zimmermann <i>et al.</i> ⁸¹

CLIA, Clinical Laboratory Improvement Amendments; CAP, College of American Pathologists; DANSR, Digital Analysis of Selected Regions; IVD, *In vitro* diagnostic product; PMA, Pre-market Approval; SNP, Single nucleotide polymorphism.

Table 2

United States patent landscape of cffDNA based noninvasive prenatal testing

Patent No.	Date of issue	Assignee	Title
US6251638	6/26/01	Diagen Corporation	Methods for detection of nucleic acid sequences in urine
US6258540	7/10/01	Isis Innovation Ltd	Non-invasive prenatal diagnosis
US6664056	12/16/03	The Chinese University of Hong Kong	Non-invasive prenatal monitoring
US6927028	8/9/05	The Chinese University of Hong Kong	Non-invasive methods for detecting non-host DNA in a host using epigenetic differences between the host and non-host DNA
US7235359	6/26/07	The Chinese University of Hong Kong	Method for diagnosing preeclampsia by detecting hCRH mRNA
US7252946	8/7/07	Zoragen, Inc.	Nucleic acid detection
US7332277	2/19/08	Ravgen, Inc.	Methods for detection of genetic disorders
US7442506	10/28/08	Ravgen, Inc.	Methods for detection of genetic disorders
US7645576	1/12/10	The Chinese University of Hong Kong	Method for the detection of chromosomal aneuploidies
US7655399	2/2/10	Boston University	Methods for prenatal diagnosis of chromosomal abnormalities
US7709194	5/4/10	The Chinese University of Hong Kong	Marker for prenatal diagnosis and monitoring
US7718367	5/18/10	The Chinese University of Hong Kong	Markers for prenatal diagnosis and monitoring
US7718370	5/18/10	Ravgen, Inc.	Methods for detection of genetic disorders
US7727720	6/1/10	Ravgen, Inc.	Methods for detection of genetic disorders
US7754428	7/13/10	The Chinese University of Hong Kong	Fetal methylation markers
US7785798	8/31/10	Boston University	Methods for prenatal diagnosis of chromosomal abnormalities
US7799531	9/21/10	University of Louisville Research Foundation Incorporated	Detecting fetal chromosomal abnormalities using tandem single nucleotide polymorphisms
US7829285	11/9/10	The Chinese University of Hong Kong	Circulating mRNA as diagnostic markers
US7838647	11/23/10	Sequenom, Inc.	Non-invasive detection of fetal genetic traits
US7888017	2/15/11	Stanford University	Non-invasive fetal genetic screening by digital analysis
US7901884	3/8/11	The Chinese University of Hong Kong	Markers for prenatal diagnosis and monitoring
US8008018	8/30/11	Stanford University	Determination of fetal aneuploidies by massively parallel DNA sequencing
US8026067	9/27/11	The Chinese University of Hong Kong	Marker for prenatal diagnosis and monitoring
US8133701	3/13/12	Sequenom, Inc.	Detection and quantification of biomolecules using mass spectrometry
US8137912	3/20/12	General Hospital Corporation	Methods for the diagnosis of fetal abnormalities
US8168382	5/1/12	The Chinese University of Hong Kong	Methods for detecting DNA originating from different individuals
US8168389	5/1/12	General Hospital Corporation	Fetal cell analysis using sample splitting
US8173370	5/8/12	Sequenom, Inc.	Nucleic acid-based tests for RHD typing, gender determination and nucleic acid quantification
US8195415	6/5/12	Stanford University	Noninvasive diagnosis of fetal aneuploidy by sequencing
US8206926	6/26/12	Sequenom, Inc.	Restriction endonuclease enhanced polymorphic sequence detection
US8288100	10/16/12	The Chinese University of Hong Kong	Methods for detecting fetal DNA in a plasma or serum sample from a pregnant woman
US8293470	10/23/12	Stanford University	Non-invasive fetal genetic screening by digital analysis
US8296076	10/23/12	Stanford University	Noninvasive diagnosis of fetal aneuploidy by sequencing

Patent No.	Date of issue	Assignee	Title
US8304187	11/6/12	Strack, Inc.	Preservation of cell-free RNA in blood samples

Patent Data are current as of December 21, 2012. Full text for patents are freely available at the USPTO website (www.uspto.gov/) or from Google patents (www.google.com/patents).

Table 3

United States patents and applications for institutions commercializing noninvasive prenatal tests

Institution	US patents	US applications
Natera ^a	0	8
Verinata Health ^b	2	19
Ravgen	4	6
NIPD Genetics	0	1
Sequenom	4	17
Stanford University	5	18
Chinese University of Hong Kong	12	18
Isis Innovation Ltd.	1	1
University of Louisville	1	5

Searches using company or institution names as 'assignees' were performed in United States patent databases to identify issued patents and pending applications. All patents and applications containing at least one claim relevant to NIPT were included. Data are complete as of 15 December 2012.

^aIncludes all applications assigned to Gene Security Network. Gene Security Network changed its name to Natera in January 2012.

^bIncludes all applications assigned to Artemis Health. Artemis Health changed its name to Verinata in April 2011.

Table 4

Major United States patents and applications associated with current and emerging noninvasive prenatal aneuploidy detection tests

Name of company	US patent/application number
Sequenom	6,258,540, ^a 6664056, ^b 6927028, ^b 7838647, 8173370
Verinata Health	7888017, ^c 80080182, ^c 8296076, ^c 8293470, ^c 8137912, 8168389
Ariosa Diagnostics	7799531 ^d
Natera	20110178719A1, 20110288780A1, 20120270212A1
Ravgen	7442506, 7718370
Trovogene	6,251,638 ^e
NIPD Genetics	US20120282613A1

Unless specified below, the company is the 'assignee' of the patent. See Table 2 for patent titles and dates of issue of patents. Detailed information for each patent and application including the full text can be obtained via the United States Patent and Trademark Office website (www.uspto.gov/).

^a Patent is assigned to Isis Innovation Ltd and is licensed exclusively and worldwide to Sequenom.

^b Patents are assigned to Chinese University of Hong Kong and licensed exclusively to Sequenom.

^c Patents are licensed exclusively to Verinata Health (previously Artemis Health) and assigned to Stanford University.

^d Patent is assigned to University of Louisville and licensed to Ariosa (previously Tandem Diagnostics).

^e Patent is assigned to Diagen, which was acquired by Trovogene.