

Background Paper: Intellectual Property and Non-Invasive Prenatal Testing in Canada

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I. The Purpose and Scope

The purpose of this background paper is to provide an overview of the intellectual property (IP) and commercialization issues associated with non-invasive prenatal testing (NIPT) in Canada. There is limited discussion and literature on the IP of NIPT within Canada, although, there are a number of papers and reports within the context of NIPT in the United States. The following brief review explores: the role IP plays in the NIPT market, the IP landscape of NIPT in Canada, and issues associated with IP protection of NIPT. It is not meant to be comprehensive. Rather, we hope it will help inform policy discussion at the workshop.

II. Background

a. What is Non-invasive Prenatal Testing?

NIPT, also known as cell-free foetal DNA (cffDNA) testing, is a relatively new process used on pregnant women to screen for specific foetal chromosome aneuploidies (Petch *et al*, 2014). In a pregnant woman's blood, there are DNA fragments in the plasma (non-cellular) compartment called circulating cell-free DNA. About 5% to 15% of a pregnant woman's circulating cell-free DNA is of placental origin and, most of the time, is identical to the fetus' genome. Circulating cell-free DNA can be analysed through technical processes associated with NIPT such as massively parallel sequencing, digital polymerase chain reaction, or relative mutation dosages.

NIPT is used to assess specific chromosomes (such as chromosomes 13, 18, 21, X and Y) for abnormalities. This technology is used as a screening test used for women who are at risk of producing a baby with a serious genetic disorder, such as Down syndrome [Trisomy 21], Patau syndrome [Trisomy 13] or Edward's syndrome [Trisomy 18] (Petch *et al*, 2014). The purpose of NIPT, when offered to women at high-risk of carrying an affected fetus, is to reduce the need for invasive testing procedures. Invasive procedures include amniocentesis and chorionic villus sampling (CVS), and are potentially harmful for the foetus and/or mother due to a chance of a miscarriage. Many studies on the performance of NIPT in high-risk women ('second tier' testing) suggest that NIPT performs very well in this scenario.

There is also the potential to use NIPT as a ‘first tier’ test for screening average-risk pregnant women, and this test could replace current prenatal Down syndrome screening approaches (Audibert and Gagnon, 2011). More clinical research is needed to assess the performance of NIPT as a first tier test, but new data is emerging. Norton et al. published the first large (15,841 subjects), industry-funded study of NIPT in the April 2015 edition of the New England Journal of Medicine. They found 100% successful detection of Down Syndrome with a false-positive rate of 0.06%. However, NIPT’s positive predictive value was only 80%. As such, NIPT is not currently considered a diagnostic test, and a positive test result must be confirmed through more established procedures (Caulfield, 2014).

Limitations to NIPT	Benefits to NIPT
Inequitable access due to cost	Lacks of risk of miscarriage
The need for further, invasive, testing due to unclear results because of two different populations of cells with different genotypes or false positives	Allows women who do not wish to terminate pregnancy a chance to have more information to utilize in preparing for an affected child
Less accurate for overweight / obese patients	Can perform the test, and receive the results, earlier than amniocentesis or CVS
Does not detect same range of disorders that amniocentesis or CVS test, and is less accurate	Can aid in the decision to go through with invasive testing

b. Overview of NIPT in Canada

NIPT was officially available in private laboratories in Canada in 2013, but only in select provinces: British Columbia, Alberta, Ontario, and Quebec. Ontario and British Columbia now provide provincial funding for NIPT, but only to expecting mothers with an elevated risk of giving birth to a baby with chromosome abnormalities (Toews, 2014; Toews and Caulfield 2014). ‘High risk’ varies between the two provinces, but is generally defined using one of the following descriptions: age (35 + years); a positive prenatal screen; a previous pregnancy with a chromosomal condition; or abnormal ultrasound findings. In Alberta, NIPT is only available to those with the same restrictions as Ontario. In British Columbia, NIPT is available to all expecting mothers. NIPT is still quite new, meaning blood samples for the purposes of NIPT are not able to be tested in Canada and must be shipped to labs in the United States or elsewhere.

III. Summary of NIPT Patents in Canada

- There is limited Canadian (or other) literature on IP rights to NIPT. To paint the Canadian IP landscape, we looked at the Canadian Intellectual Property Office (CIPO) patent database, industry reports, newspapers and other media outlets, and peer-reviewed literature.
- Companies from the United States, Europe (Netherlands, France, Germany, Italy, Switzerland, Cyprus), Australia, and Asia (China, Israel) have Canadian patents filed for their respective NIPT processes.
- The four companies from the United States - Sequenom, Verinata Health, Natera, and Ariosa - and the Chinese University of Hong Kong have filed the majority of NIPT patent applications in Canada. Sequenom appears to be the only company issued a patent for a NIPT process in Canada (number 2282793, filed in 1998 and issued in 2010). The equivalent patent in the United States is attributed as the first official NIPT patent, invented by Dennis Lo (Agarwal *et al*, 2013).

Statements from literature on the tensions of IP protection for NIPT

“Innovation remains costly, with NIPT tests still costing near \$1000...” – Dimond P F, Gen Engineering and Biotech News, 2015

“Illustrative of the competitive climate for these tests are ongoing patent fights. ...As a result, [the 3 competing US companies] have all sued Sequenom, arguing that slight differences in their testing methods do not constitute infringement.” – Dimond P F, Gen Engineering and Biotech News, 2015

IV. The Role IP Plays in the NIPT Industry

- All NIPT related patents, which include patents specific to cffDNA and foetal aneuploidy, patent specific processes used for NIPT. No form of biological matter (e.g. DNA) is legally claimed in a NIPT related patent (Chandrasekharan, 2013).
- IP protection affects NIPT’s market worth, and this market is becoming visibly lucrative. A market report published by Transparency market Research predicts the NIPT market will grow from 0.53 billion USD in 2013 to 2.38 billion USD in 2022 (Marketers Media, 2015). Owning a patent ensures that the respective company will play a role in the development of the NIPT market (Chandrasekharan, 2013).
- Companies that do not own NIPT patents gain access to NIPT technology by partnering with one of the aforementioned companies. For example, LabCorp (an American company) partnered with Verinata and generated its own test using Verinata’s patented NIPT technology (Karow, 2015).
- There are other companies that have not developed their own test, and merely partner with a company that holds a patent for a NIPT process to facilitate offering NIPT as a service. For example, in Ontario, Life Labs uses Natera technology (Panorama), Medcan Clinic uses Verinata technology (Verifi), and Gamma-Dynacare

uses Ariosa technology (the Harmony Prenatal Test) to offer NIPT as an option to pregnant women (CHEO, 2014).

V. Potential Impacts of NIPT IP to Canadian Health Care and NIPT Development

- In the context of NIPT, it is important to keep in mind the public purpose of a patent: to encourage innovation. This is done by providing the owner of an invention with an exclusive right of control, i.e. a limited monopoly. This trade off – that is, the higher costs associated with the granting of monopoly – is theoretically, in the aggregate, good for society. Patents require the holder to disclose his/her invention so that others can build on his/her work, further facilitating innovation. Finally, patents are also justified as a way to enable investment (Knudsen and Vogd, 2015).
- Issues associated with protecting NIPT through IP include: reduced market competition and subsequently poor quality assurance, decreased availability of cheaper alternative tests, and/or reduced cost effectiveness (Agarwal *et al*, 2013). In the UK, Premaitha Health has gainsaid possible patent infringement and developed its own cffDNA test without licensing the techniques from Illumina. Premaitha's CEO says that this test and associated agreements to supply it will "accelerate the broad dissemination of NIPT in Europe" (Genomeweb, 2015). Illumina has filed a suit seeking damages and an injunction; if successful, it will likely be a clear example of patent law causing public disservice.
- Lawsuits can be another issue. All four American companies are involved in patent infringement lawsuits against one or more of each other. However, Sequenom and Illumina (the company who owns Verinata) agreed to pool their NIPT IP in late 2014 - a positive litigation outcome. This triggered a jump in the global number of health providers offering NIPT services, and coincided with the beginning of a shift from a

"If Sequenom, or anyone else, has a patent-enforced monopoly on providing NIPT in the US, the technology will be more expensive, will expand more slowly, will improve more slowly, and will help fewer women than if there is effective competition" – Greely H, Stanford Law School, 2013

"...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..." – Judge Illston, USDC, 2012

"...must determine whether the claimed processes have transformed these unpatentable natural laws into patent-eligible applications of those laws." – Justice Breyer, USSC, 2011

"...phenomena of nature, though just discovered... are not patentable, as they are the basic tools of scientific and technological work... And monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it." – Justice Breyer Quoting *Gottschalk v Benson*, USSC, 2011

"...claims covering these [methods for analyzing DNA] diagnostics could be harder to 'invent around'" – Chadnrasekharan S, Duke Global Health Institute, 2009

focus on mostly high-risk patients to one on much more numerous average-risk patients (Karow, 2016).

- The outcome of a lawsuit, and as such the overall look of an industry landscape, is unpredictable. For example, in June 2015, the U.S. Court of Appeals for the Federal Circuit in *Ariosa Diagnostics, Inc., Et Al. v. Sequenom, Inc., Et Al* upheld the decision that Sequenom's existing '540 patent for an NIPT test was invalid because it merely applied well-known existing testing techniques to a novel natural discovery (cffDNA) (Boetticher, 2015). This changes the entire American NIPT landscape, and will likely be petitioned to the Supreme Court.
- In the NIPT industry there is worry that a single company (e.g. Sequenom) could acquire a market monopoly by successfully securing injunctions on all competitors (Agarwal *et al*, 2013). This would hinder access and/or increase costs. For example, if a company attains a monopoly and only has agreements with certain third parties (e.g. select insurance companies, or select health care providers) some members of the public could be left at a disadvantage in accessing the patented technologies. For example, in Canada, a pregnant woman in Manitoba has to travel to gain access to NIPT, as only select health care providers in BC, Alberta, Ontario and Quebec have the legal partnerships necessary to provide the service.
- IP protection can create high costs when research and development costs are high due to inventing around other patents, when there are numerous lawsuits, or when royalty fees are implemented. All three of these factors contribute to the high cost of NIPT. The price tag attached to a non-invasive prenatal test is between \$700 and \$950 in Canada. It should be noted, however, that IP is only one reason associated with the high cost. Other drivers include, for example, the fact that Canada has to ship blood samples to the United States for testing (Petch *et al*, 2014), and the way blood samples are tested, e.g. via massively parallel sequencing, PCR, or relative mutation dosages (Lo, 2012).
- Patents on NIPT processes can also hinder access to other research institutions. The development of innovative technologies for NIPT is slowed by decreasing access for research purposes, as it is difficult to develop a technology without access to it (Greely, 2013).
- Another concern is that, as the NIPT industry grows and companies find ways to test for single-gene disorders, the gene a company wishes to look at may already be subject to a patent for a gene sequence or mutation. The result would be increased difficulty in developing NIPT technology and securing rights for such technology (Agarwal *et al*, 2013). Note that the issues associated with NIPT patents are *not* connected to the issues with gene patents. Indeed, we need to be careful not to conflate the issues associated with gene patenting more broadly with those associated with NIPT. This bullet point is merely used to explain how it could be

difficult to patent a NIPT process that may target a gene sequence or mutation protected by IP.

- Concern for IP in the NIPT domain raises questions about science policy's paradox between, on one hand, the push to commercialize work, and on the other, the aim to ensure access to technologies and information.
- An Albertan MP expressed that, “we are trying to get funding [for NIPT]... we're between a rock and a hard place – being obliged to offer a test that the patient has to pay for. That's a no-no in the Canadian health-care system...” (Swift, 2014). Governments want the public to have full access to NIPT but are pushing NIPT companies to commercialize, which means they are encouraging patenting and indirectly causing the cost of NIPT to stay high.

VI. Conclusion

There are still many questions when it comes to protecting NIPT technologies through IP, including: (1) How much will IP hinder public access to NIPT in Canada? (2) Is IP the best means to protect NIPT technologies? (3) What are other ways to both protect NIPT technologies and encourage access and knowledge sharing? (4) How will IP protection hinder further research and development of NIPT in Canada? This background paper is only meant as an initial overview of NIPT's IP landscape and the related issues. Further research and discussion will be required as the NIPT market grows in Canada.

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