The Market in Noninvasive Prenatal Tests and the Message to Consumers: *Exploring Responsibility*

by KELLY HOLLOWAY, NICOLE SIMMS, ROBIN Z. HAYEEMS, and FIONA A. MILLER

Table 1.
Number of Entities Offering Distinctly Branded NIPTs by Location

Headquarters location	*Number of entities*	*Number of tests offered*
United States	18	25
Australia	4	6
China	4	6
India	4	5
Taiwan	3	9
Germany	3	8
Italy	3	13
Spain	3	5
United Kingdom	3	3
Korea	2	2
Singapore	2	3
Switzerland	2	3
Belgium	1	1
Cyprus	1	1
France	1	2
Portugal	1	1
Russia	1	1
South Africa	1	1
Total	**57**	**95**

Table 2.
Entities with English-Language Brochures

For-profit entities (n = 27) and their tests (for brochures, n = 28)	*Nonprofits (n = 5)*
Agilent—Clarigo	Arup—NIPT
Ariosa—Harmony	GOSH—SAFE
BGI—NIFTY Pro	NHS United Kingdom—Lucina
Bioarray—NIPT	UZ Leuven—NIPT-PLUZ
Centogene—CentoNIPT	VGCS—Percept
CGC Genetics—Tomorrow	
Counsyl—Prelude	
EVOLVE—NIPT	
Eurofins Biomnis—Ninalina	
Genea—GeneStyle	
Genesupport—Fasteris	
Genoma—Tranquility, PrenatalSAFE Karyo (2)	
Genomic Diagnostic—Generation	
Igenomix—NACE	
Illumina—Verify	
INEX—iGeneScreen	
Integrated Genetics—InformaSeq	
Lab Genomix—Determine 10	
Lifecodexx—Prenatest	
Mygenetx—MyNIPT	
Natera—Panorama	
NIM Genetics—TrisoNIM Premium	
NxGen—Informed	
Premaitha—Iona	
Quest—Qnatal	
Sequenom—MaterniT Genome	
Veritas—myPrenatal	

Table 3.
English-Language NIPT Brochures' Compliance with Nuffield Council on Bioethics Criteria

Nuffield importance rating	*Nuffield category*	*Nuffield category elements*[1]	*Compliance*		
			All	*For-profit entities*	*Nonprofits*
Essential	Test performance	The test is clearly presented as screening (versus diagnostic).	48%	43%	80%
		Sensitivity and PPV are provided for each condition.	18%	18%	20%
		Claims are based on recent, high-quality, peer-reviewed clinical data.	30%	36%	0%
	Follow-up diagnostic testing	The description clearly states that positive results must be confirmed through diagnostic testing.	70%	64%	100%
		The description clearly states that follow-up testing is entirely up to the woman.	39%	36%	60%
		NIPT is not represented as a replacement for invasive testing.	45%	36%	100%
	Test failure	The description clearly states that test failure is possible.	58%	50%	100%
		A figure for the likelihood of test failure is provided.	33%	36%	20%
		A course of action in the event of test failure is articulated.	27%	18%	80%
	Description of genetic conditions	Genetic conditions are described using neutral language.	27%	29%	20%
		Links to reliable information about genetic conditions are provided.	15%	11%	40%
Good practice	Implications of testing	The description clearly states that the test may lead to difficult decisions.	36%	32%	60%
		The test is not represented as offering "reassurance" or "peace of mind."	61%	57%	80%
	Services offered	The description clearly states what pre- and posttest counseling or support services patients can expect from the company.	61%	57%	80%
		The format and timing of results are described.	42%	39%	60%
		Average compliance	**41%**	**37%**	**60%**

[1]See table S1 in the methods supplement for a discussion of the researchers' interpretation of each element.

Table 4.
English-Language NIPT Brochures' Compliance with All Three Nuffield Council Criteria Related to Establishing NIPT as a Screening (versus Diagnostic) Test

Nuffield importance rating	*Nuffield category*	*Nuffield category elements*[1]	*Compliance*		
			All	*For-profit entities*	*Nonprofits*
Essential	Test performance and follow-up diagnostic testing	The test is clearly presented as screening (versus diagnostic). The description makes clear that positive results must be confirmed through diagnostic testing. NIPT is not represented as a replacement for invasive testing.	30%	21%	80%

[1]See table S1 in the methods supplement for a discussion of the researchers' interpretation of each element.

Table 5.
Forms of Regulation Mentioned in NIPT Brochures (%)

Form of regulation	*For-profit entities*	*Nonprofits*
Statutory approval (CE mark)	21%	20%
Laboratory regulation approval	46%	20%
Clinical practice guidelines	32%	0

Methods

1. Mapping of global NIPT market:

In order to answer the question of what NIPT tests are currently marketed globally, we began with a review of scholarly papers that reported on the major companies in this industry (Agarwal 2013, Minear, Allyse). We then used industry articles and reports acquired through a search of the words "non-invasive prenatal test" and "cell-free DNA test" in the Capital IQ Database (a market intelligence platform consisting of technology and financial services data from public and private companies). Finally, we did an internet search for NIPT companies. A database of NIPT companies was developed and populated with key information for each company, including company name, headquarters, company type (for-profit/nonprofit), test name(s), conditions targeted, etc. We focused on independently branded NIPTs. Thus, NIPT companies that resell tests under another company's brand were excluded (for example, many companies offer Ariosa's Harmony test or Natera's Panorama test); however, companies that offer NIPTs under their own brand were included, even where the test was developed by another company. Companies that solely manufacture/market NIPT analysis platforms or software (rather than the tests themselves) were also excluded.

2. Qualitative analysis of patient brochure content:

Using MAXQDA, a software for qualitative content analysis, we conducted qualitative coding of 33 English-language patient brochures from 32 companies that offered patient brochures (one company, Genoma, markets two distinctly-branded NIPTs in different markets).

2.a) Nuffield Criteria

In 2017, the Nuffield Council undertook a review of the ethical issues raised by the increasing use of NIPT, the results of which appear in the report "Non-invasive prenatal testing: ethical issues." Based on the concerns

articulated in this report, Nuffield developed a supplementary guidance document for manufacturers and healthcare providers titled “Information to include on your website and patient leaflets about non-invasive prenatal testing (NIPT),” some of which is “essential,” and some of which should be provided “as a matter of good practice.” We used this guidance document to develop a checklist that would allow us to analyze the adequacy of the content of NIPT brochures. In some cases, applying the Nuffield criteria was straightforward; in others, we had to interpret the criteria in order to operationalize them; we indicate how we made these interpretive decisions in Table S1. We then assessed whether the content of each brochure was “compliant” or “uncompliant” with each criterion as we had interpreted it.

Some of the Nuffield recommendations were not included in our analysis. One reason is that the information was not relevant for our analysis – for instance, the requirement that a hospital or clinic providing the test would inform patients about how it would offer follow-up diagnostic testing and at what cost was not assessed as very few of the entities in question were hospitals or clinics. Another reason that some Nuffield recommendations were not included is that they had close to 0% alignment in all brochures. For instance, Nuffield mandates that companies clarify whether the test will reveal information about the mother’s genetic make-up, and if so, any policy on providing secondary findings to the mother; however, it was not clear whether the tests had the capacity to uncover secondary findings. Nicole Simms and Kelly Holloway conducted independent coding using the criteria developed, then met to perform intercoder agreement resolving disagreements through discussion.

Our analysis of the brochures found considerable overlap between three of the Nuffield criteria: the test is clearly presented as a screening test; it is clear that positive results must be confirmed through diagnostic testing; and NIPT is not represented as a replacement for invasive testing. Thus, in our analysis we considered these criteria separately, then combined them to determine compliance with the provision of an accurate representation of NIPT as a screening test.

Our analysis of Nuffield's pre- and post-test counselling required some interpretation. Although every brochure offered a website URL and/or phone number through which patients could access further information, we counted only explicit mentions of pre- and post-test "counselling" or "support" (rather than "information") in reference to this directive. We determined that it was clear whether or not a company would provide pre- and/or post-test counseling/support services if: 1) patients were directed to the company's own website or representatives (via a phone number) for counseling/support, indicating the company offered these services 2) patients were directed to their healthcare provider and/or a genetic counselor for counseling/support, indicating the company did not offer these services. Brochures were only deemed uncompliant with this directive if they made no mention at all of where patients could obtain pre- and/or post-counseling.

Table S1: Interpretation of Nuffield Guidelines

NUFFIELD IMPORTANCE RATING	NUFFIELD CATEGORY	NUFFIELD CATEGORY ELEMENTS	OUR INTERPRETATION OF NUFFIELD GUIDANCE
ESSENTIAL	Test Performance	Test is clearly presented as screening (vs. diagnostic)	The test is consistently referred to as a screening test, and it is specified that it is not a diagnostic test.
		Sensitivity and PPV values of the tests on offer are provided for each condition	Values for both sensitivity and PPV are provided for each condition tested for.
		Claims are based on recent, high quality, peer-reviewed clinical data	As Nuffield did not offer guidance on interpretation of this point, researchers decided that the brochure was in alignment with it if at least one source was cited.
	Follow-up Diagnostic Testing	Clear that positive results must be confirmed through diagnostic testing	It is specified that positive results can be confirmed only with diagnostic testing.
		Clear that follow-up testing is entirely up to the woman	It is clear that the decision to pursue follow-up testing is the woman's.
		NIPT is not represented as a replacement for invasive testing	NIPT is not characterized as an alternative to or on par with invasive testing; claims that NIPT allows women to "avoid" invasive testing must clearly indicate this applies only to women who receive negative results.

	Test Failure	Clear that test failure is possible	It is clear that the test may yield “no result” (mention of false positives/negatives is insufficient).
		A figure for likelihood of test failure is provided	A figure indicating the likelihood the test will yield “no result” is offered.
		Course of action in the event of test failure is articulated	A clear course of action in the event of a “no result” test is articulated.
	Description of genetic conditions	Genetic conditions are described using neutral language	The language used does not depict genetic conditions in a negative light (Nuffield offers the following examples: “chance” should be used instead of “risk”; a fetus should not be said to “suffer” from a genetic “abnormality”).
		Links to reliable information about genetic conditions are provided	At least one source or organization to which patients can turn for more information is offered.
GOOD PRACTICE	Implications of testing	Clear that test may lead to difficult decisions	There is some discussion of the decisions that will have to be made in the event of a positive NIPT - this could include an immediate decision about whether or not to proceed with confirmatory invasive diagnostic testing (which carries a small risk of miscarriage), and/or a decision about the pregnancy more broadly if follow-up testing is also positive. It is also sufficient if there is a recommendation that patients consider their own values etc. before taking the NIPT.
		Test is not represented as offering "reassurance" or "peace of mind"	The utility of the test is expressed in a neutral manner; that is, that it can offer the patient information about the fetus. Characterization of the test as reassuring is acceptable if it is specified that this is only in the event of a negative result.
	Services Offered	Clear what pre and post-test counseling/support services patients can expect from the company	There is some mention of how to access counseling/support. If the company mentions it provides counseling, patients can expect to receive counseling from the company. If the company mentions the patient should seek counseling from their doctor and/or genetic counselor, the patient can expect to receive no counseling from the company.
		The format and timing of results are described	The brochure offers some indication of what the results will look like (i.e., "negative or positive” or “high, medium, or low”) AND when the patient can expect to receive them (i.e., 5 days).

2.b): Concept-driven coding of patient brochures

In order to assess how NIPT companies seek to substantiate the efficacy, safety, and overall legitimacy of their products in the absence of formal regulatory test approval, we also conducted a separate qualitative analysis. This analysis began with a review of the literature in this area, and familiarization with relevant regulations governing NIPT. We then undertook concept-driven coding focusing broadly on regulation and professional authority. Nicole Simms conducted interpretive coding of the brochures with particular attention to these concepts. This process yielded 230 discrete codes, grouped into the following thematic categories: experts; importance of the test; regulatory approvals; post-test options; test claims; disclaimers and test results. The most prevalent themes not already explored through our coding of Nuffield's criteria were experts and regulatory approvals. Nicole Simms counted the number of brochures that contained these two themes and represented them as a percentage of the overall number of brochures.

For both of these analyses, we compared brochures from for-profit and nonprofit entities to ascertain any distinctions in, first, their compliance with the Nuffield criteria, and second, themes related to test legitimacy. This comparison was undertaken in an attempt to determine whether the profit motive of for-profit NIPT companies has any bearing on how their tests are represented in marketing materials.

2.c) Comparison of commercial and non-profit

In order to answer the question of whether there are differences between NIPT brochures produced by commercial and non-commercial entities, we compared the information provided by commercial companies to that offered by non-profit laboratories producing the test. Where possible, we used the Capital IQ database to establish company type. In instances in which this was not possible, we sought out relevant information on company websites; VCGS, for example, was not listed in Capital IQ, but the first line on its site states that it "is a not-for-profit provider of specialist genetics clinical services throughout Victoria, Tasmania and the Northern Territory." The other providers that qualified as nonprofit were ARUP, UZ Leuven, and the UK's National Health

System (NHS), which offers both the Lucina and SAFE tests (through different public hospitals). All of the nonprofit tests were affiliated with a public hospital in their respective jurisdictions.

Limitations

First, the complexity and opacity of licensing practices make it challenging to determine whether a given company is offering a discrete, proprietary assay, or a licensed/rebranded test. A given NIPT can be sold in multiple markets under different names, but because marketing may differ by jurisdiction and each market is potentially subject to distinct regulatory requirements, we elected to include all companies offering distinctly branded NIPTs in our analysis.

Second, we only analyzed consumer brochures. There is relevant consumer-directed information on the companies' website which is not included in this analysis. However, upon reviewing the websites and brochures, it was clear that the brochure was a distilled representation of the website content, and therefore we felt it served as an appropriate representation of the company's message.

Third, there were so few (n=5) brochures from non-profit companies in the analysis that the final nonprofit percentages indicating compliance with Nuffield or invocation of regulatory bodies could seem misleading. The comparison between for-profit and non-profit entities was only a minor part of the analysis, however, and serves only to allude to an issue that is already well-substantiated elsewhere – the impact of commercial interests on the accuracy of information offered in medical marketing materials.