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Informed decision-making about prenatal cfDNA screening: An assessment of written materials

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Abstract

Objectives—The introduction of prenatal cfDNA screening for fetal aneuploidy and other genetic conditions has exacerbated concerns about informed decision-making in clinical prenatal testing. To assess the information provided to patients to facilitate decisions about cfDNA screening, we collected written patient education and consent documents created by laboratories and clinics.

Methods—Informed consent documents (IC) were coded by two independent coders. Each IC was assessed for readability, attention to elements of informed consent, and completeness of information about the test and the screened conditions.

Results—We found variance between IC produced by commercial laboratories versus those provided by local clinics or health care systems, and considerable variance among materials from all sources. “Commercial” IC were longer and written at a more difficult reading level than “non-commercial” IC, and were less likely to state explicitly that cfDNA only screens for certain conditions. About one-third of IC were combined with laboratory order forms. Though most IC recommended confirmatory testing for positive results, only about half clearly stated that results could be incorrect—including mentions of false positives or false negatives. About one-third of IC explicitly stated that cfDNA screening was optional. While nearly all IC from any source listed the conditions screened by the test, only about half of the IC included any phenotypic descriptions of these conditions. Few IC mentioned psychosocial considerations, and only one IC mentioned the availability of support groups for families of children with genetic conditions.

Conclusions—Based on our findings, we recommend that written and well-informed consent be sought before performing cfDNA screening, and we offer minimal and recommended standards for patient education and consent materials.

Conflicts of Interest

The authors report no conflicts of interest.

Abstract

L'introduction du dépistage prénatal cfDNA aneuploïdie fœtale et d'autres maladies génétiques a exacerbé des préoccupations au sujet de prise de décisions éclairée dans les cliniques de dépistage prénatal. Afin d'évaluer les informations fournies aux patients pour faciliter les décisions sur le dépistage de la cfDNA, nous avons recueilli patient education et consentement écrits émanant des laboratoires et des cliniques.

Les documents de consentement éclairé (IC) ont été codées par deux programmeurs indépendants. Chaque IC a été évaluée pour la lisibilité, attention aux éléments du consentement éclairé et l'exhaustivité des informations sur le test et les conditions de dépistage.

Nous avons trouvé la variance entre IC produite par les laboratoires commerciaux par rapport à ceux fournis par les cliniques locales ou des systèmes de soins de santé et écart considérable entre les matériaux de toutes les sources. IC "Commercial" étaient plus longs et écrite à un niveau de lecture plus difficile que IC « non commerciales » et étaient moins susceptible d'État explicitement ce cfDNA seulement des écrans pour certaines conditions. Environ un tiers d'IC ont été combinées avec les bons de commande de laboratoire. Si IC plus recommandés pour les résultats positifs des tests de confirmation, seulement environ la moitié a clairement indiqué que les résultats pourraient être incorrectes — y compris les mentions de faux positifs ou faux négatifs. Environ un tiers des IC a explicitement déclaré que cfDNA dépistage était facultative. Tandis que presque tous les IC de n'importe quelle source répertorié les conditions examinées par le test, seulement environ la moitié du ci inclus toute description phénotypique de ces conditions. IC peu mentionné les facteurs psychosociaux et seul IC mentionné l'existence de groupes de soutien pour les familles des enfants atteints de maladies génétiques.

D'après nos résultats, nous recommandons que le consentement écrit et bien informé peut rechercher avant d'effectuer le dépistage des cfDNA, et nous offrons des normes minimales et recommandées pour l'éducation du patient et consentement des matériaux. Une de nos neuf recommandations est que quelle que soit la question de savoir si une signature est requise, les documents de consentement éclairé devraient inclure une instruction simple consentement ne pas associée à des accords juridiques ou financières. Figurant en bonne place devrait être aussi le nom et les coordonnées d'un fournisseur local de clinique qui est disponible pour d'autres questions.

English Keywords

cfDNA; NIPT; prenatal screening; informed consent; reproductive health

French Keywords

cfDNA; NIPT; dépistage prénatal; consentement éclairé; santé de la reproduction

Introduction

Prenatal genetic screening using cell-free DNA (cfDNA) became commercially available for clinical use in late 2011. Often called non-invasive prenatal testing or screening (NIPT or NIPS), cfDNA screening has expanded rapidly: in numbers of conditions screened by each

assay; in geographic availability, now virtually worldwide; and in scope of clinical practice, now potentially offered for any pregnancy regardless of *a priori* risk for fetal conditions (1–3). The increasing popularity of cfDNA screening has been propelled, at least in part, by its advantages over previously available screening and diagnostic testing: it requires only a maternal blood sample; it can theoretically be performed earlier in gestation; and, for certain genetic conditions, it is more accurate than previous screens (4). However, the introduction and rapid adoption of prenatal cfDNA screening has exacerbated concerns about informed decision-making for clinical prenatal testing. These concerns include the influence of aggressive commercial marketing and media hype about cfDNA screening, the increasing amount of information that pregnant women/couples are expected to absorb during the prenatal period, and the routinization of genetic testing in prenatal care, especially in light of the minimal procedural risk involved in cfDNA screening (5, 6).

It is tempting to think of cfDNA screening, much like more standard serum screens, as a test for which written informed consent is unnecessary; indeed, some health care providers consider written consent less important for cfDNA screening than for diagnostic testing such as amniocentesis (7). However, as cfDNA screening expands, it forces women and families to confront ever more challenging deliberations about whether to have prenatal testing and how to deal with test results (8–10). Because of the ease of a blood draw and the early gestational stage at which it is often performed, many patients may lack not only understanding of the purpose of cfDNA screening, but also awareness that it may lead to difficult decisions about pregnancy management, invasive testing, family quality of life, and pregnancy termination (8, 11–14).

Due to these concerns, ethicists have recommended that informed decision-making practices for cfDNA screening should resemble those for prenatal diagnostic testing (12, 15, 16). As the scope of cfDNA screening continues to expand (1, 3, 17), the informational load of testing on patients will continue to rise, along with the possibility that patients and families will make pregnancy decisions based on inadequate information about test results, test limitations, and screened conditions (6, 18–20). However, with multiple competing companies offering cfDNA screening and few standards for educating patients and guiding informed decision-making, it is not clear what information patients are utilizing to make cfDNA screening decisions. In order to better understand the information guiding patient decisions, we evaluated written informed consent documents for cfDNA screening, and have provided recommendations to improve the informed consent process.

Background

Informed consent for a health care decision requires a competent individual to voluntarily and intentionally, without substantial external control, authorize a professional to perform a plan or procedure (21, 22). An informed choice is based on adequate and high-quality information, allows individuals to weigh multiple options, and reflects the decision-maker's values (23, 24). A 1982 report from the US President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research concluded that an informed decision-maker must have substantial relevant knowledge and understanding of the health care intervention in question (including the indications for the intervention, available

alternatives, possible risks and benefits, possible costs and consequences, and significant uncertainties about any of this information) and is fundamentally entitled to accept or reject it (25). Although the normalization of consent practices in health care has often resulted in legalistic documents that protect the interests of institutions, the ethical imperative of informed consent is a process of conversation and consideration, rather than a single signed document, and ideally nurtures patient well-being, empowerment, and trust (21, 26). However, written information often helps patients assimilate information at their own pace, and signing a document may provide them an opportunity to reflect upon and exercise their free choice (8, 25, 26).

Several professional clinical societies have issued recommendations for the implementation of cfDNA screening, and all include mention of informed decision-making (27–30). All of these recommendations agree that cfDNA screening is a high-quality screening test for certain fetal aneuploidies, particularly in populations at elevated risk for those conditions; that when cfDNA is offered, patients should be counseled with information about the test and its benefits and limitations; and that positive results should be followed up with genetic counseling and confirmed with diagnostic testing. Though early recommendations endorsed the offer of cfDNA screening only in cases of elevated risk for aneuploidy, more recent studies have validated cfDNA screening in average-risk populations, and the most recent professional recommendations have recognized cfDNA screening as a permissible option for the general obstetric population, though not as a standard first-tier screen (29–31). As of 2016, no professional society has made specific recommendations for written informed consent documents. However, in 2012, Allyse and colleagues developed a set of ethical best practices for the provision of cfDNA screening, which recommended that after pre-test counseling, patients should review and sign a documentation of their consent or refusal, and that this document should include:

- (1) a list of indicated tests that patients may choose to undergo; (2) a description of all possible findings and their validity (including the potential for assay failure), utility, and limitations; (3) a list of alternative tests for similar indications if applicable; and (4) options for patients who do not wish to receive all results.(15)

More recently, the European and American Societies of Human Genetics (ESHG and ASHG, respectively) issued a joint policy statement on “responsible innovation” in cfDNA screening, echoing the need to avoid routinization and facilitate informed decision-making with counseling and education, and calling special attention to the needs of patients whose language, culture, or health literacy may differ from those of the clinician or majority population (16).

In the context of cfDNA screening, fully informed consent requires at least some knowledge of the conditions being screened, which ideally includes some idea of the range of clinical phenotypes and the quality of life that affected individuals and their families may expect (15). The information parents are offered about genetic conditions should be up-to-date, accurate, and balanced—particularly because potential parents make termination decisions against a backdrop of consistent societal bias against those with disabilities (32–34). Evidence suggests that cfDNA screening could lead to increased pregnancy terminations (35, 36); indeed, nearly 15% of surveyed genetic counselors indicated they had at least one

patient terminate a pregnancy in their clinic based on cfDNA screening results alone (37). Bias concerning disability, both among health care providers and in public opinion, may influence such decisions (38–41). However, assumptions about the costs, limitations, and suffering associated with disability often do not reflect the experiences of those living with disability. For example, a US study found that most mothers of children with Down syndrome reported high overall family functioning (42); and a UK study of individuals living with Down syndrome found that they viewed their lives as rewarding and attributed problems less often to their genetic condition than to social barriers, such as a lack of opportunities and income (43). The wide variability of phenotypes within and among conditions that may be detected with cfDNA screening means that few patients will know precisely what to expect when a particular condition is detected, and that informed decisions will require the availability of balanced, family-relevant information about these conditions.

The need for adequate patient education and informed decision-making support is pressing, given the rapid integration of cfDNA screening into prenatal care and a strong preference for noninvasive prenatal testing. US studies have found strong support among pregnant women and the general public for cfDNA screening, emphasizing that they value its noninvasiveness, accuracy, early timing, testing ease, and the ability to determine fetal sex (8, 44). However, research has shown that women's choices in prenatal screening are strongly influenced by the attitudes of health care providers and the way screening is described by both providers and informational pamphlets (22). And a recent study found that patient educational materials from US laboratories offering cfDNA screening had high reading levels and were not congruent with content recommendations from professional organizations (45). The present study examines informed consent documents for cfDNA screening from a variety of sources, assessing the components of information provided and offering recommendations for improving the consent process.

Methods

Informed consent documents (IC) were collected between March and December of 2014. Documents were collected through professional contacts with individual clinics or clinicians (n=21), through Internet searches (n=69), and via a request posted to an email list for prenatal genetic counselors (n=3). Dates on documents, when available, ranged from 2012 (no month identified) to October 2014. Documents were included if they were in English (or were multilingual including English), and either: (1) included a consent statement for cfDNA screening with a signature line; or (2) were otherwise clearly identified as patient information sheets for cfDNA screening. Advertising brochures from laboratories were excluded unless they also included a patient consent statement with a signature line. Documents were excluded from the final coding set if they did not meet the inclusion criteria above, or if they substantially duplicated another document in the coding set.

Four of the authors collaboratively developed a codebook, then iteratively refined it by successively coding two test documents independently and editing the codebook by consensus after each test coding. One author and another independent coder coded all documents using this codebook. Most information was coded as either present or absent (yes/no). Information about screened conditions was coded 0 if absent; 1 if the condition

was mentioned but not described; and 2 if the condition was described, including phenotype. When documents contained information that was not directed to patients (e.g., laboratory order forms), only the portion of the document directed to the patient was coded. Results from the two coders were compared using either Cohen's kappa (for yes/no codes) or weighted kappa (for codes with 3 options). Codes with kappas of 0.6 or below were re-coded after re-training on the meaning of the code. Three codes had an unusually low kappa (0) despite near-unanimous agreement, due to a well-known paradox in Cohen's kappa; the discrepancies in these two codes were reconciled manually by the two coders and removed from the final kappa average. Final kappas averaged 0.84, with a range of 0.61–1.00. Any remaining discrepancies were then manually reconciled by a third coder to achieve final coding decisions for each document. Flesch-Kincaid reading grade level (to estimate reading difficulty) was also assessed, by pasting document content (minus headers, footers, and content not directed to the patient) into the website: readability-score.com.

Results

Sample

We collected a total of 93 informed consent documents (IC). Of these, 61 were discarded because they were duplicates or because, upon review, they did not meet the inclusion criteria. The final coding set thus consisted of 32 IC (see Table 1). About half (n=15) were from the US, and the rest were from 10 other countries (see Figure 1).

Commercial vs. Non-Commercial IC

We categorized 22 documents as “Commercial IC” (produced by a commercial laboratory for broad distribution) and 10 as “Non-Commercial IC” (produced by a local clinic or health care system for their own patients). (See Table 2.) Commercial IC were typically longer and written at a more difficult reading level than Non-Commercial IC; these readability differences are partially due to the fact that Commercial IC often included legal disclosures and financial responsibility statements, which were sometimes lengthy and complex. For example, Commercial IC often devoted space to information about laboratory certification and/or about sample retention and use, which is regulated in some jurisdictions. Commercial IC more often cited the high sensitivity of cfDNA screening, particularly for trisomy 21 (Down syndrome); however, Commercial IC also much more often listed limitations on the use of cfDNA screening (most often limitations on multiple gestations), and more often noted that cfDNA is optional and that post-test genetic counseling is an option. Non-Commercial IC more often stated the cost of cfDNA screening and mentioned the possibility of assay failure—which can occur when the sample does not contain sufficient DNA from the fetus or placenta, or for other reasons that are not fully understood.

IC format

About one-third of IC (n=11) were combined with a laboratory order form. This format occurred in both Commercial IC and Non-Commercial IC. The format varied, but typically consisted of a single document with a laboratory order form—including a brief patient consent to be signed—on the front, and more detailed patient information on the back. Two of these 11 forms did not include any detailed patient information; in both cases, however,

the patient was directed to sign an acknowledgement that she had received information about the test from her provider—suggesting that these forms were intended to be distributed with accompanying materials. The IC that were combined with laboratory order forms often crowded a great deal of information into one document, and portions directed at the patient were sometimes interspersed with instructions for clinicians ordering the test. Thus it was frequently unclear whether patients were given a copy of this information to take home. Among all IC, the patient was specifically directed to keep a copy of the IC in only two cases (one IC that was combined with a laboratory order form, and one that was not).

Information about test capabilities, results, limitations, and complications

Professional guidelines all confirm that cfDNA is a screening test that is not diagnostic. The phrases “not diagnostic” and “screen”/“screening test” appeared in 15 and 19 IC, respectively (see Table 3). About one-third of IC (n=10) mentioned alternative tests (including diagnostic tests), and only half of these gave any description of these alternatives. As noted above, most IC mentioned that there are circumstances when cfDNA screening cannot be performed, which (depending on the specific test) can include multiple gestations, pregnancies from *in vitro* fertilization, consanguinity, prior bone marrow transplants in the mother, and certain parental genetic anomalies. Most IC (n=24) also noted the gestational age when cfDNA screening could be offered, usually 9 or 10 weeks.

The format of test results from cfDNA screening varies, with some tests returning a risk score and others returning simpler results such as “Aneuploidy (not) detected.” A majority of IC (n=19) mentioned the format in which test results would be delivered, and half (n=16) stated the person to whom test results are returned (usually the health care provider). Most IC (n=28) recommended confirmatory testing for positive results, though fewer (n=23) clearly stated that results could be incorrect, including mentions of false positives or false negatives (see Table 3).

Specific numbers for either test sensitivity or specificity were mentioned in over one-third of IC (n=13); however, no IC offered information on the positive or negative predictive values (PPV or NPV) of cfDNA screening, either explicitly by these names or in a lay explanation. A few IC (n=4) mentioned that testing could uncover incidental genetic findings about a parent, and none indicated whether this information would be reported to the patient. No IC mentioned that testing may reveal tumors or cancer in the mother (see Table 3).

Information about screened conditions

Conditions screened by cfDNA vary; while all the tests represented by our sample screened for trisomies 21, 18, and 13, some tests screened for many more—including fetal sex, sex chromosome aneuploidies, and select microdeletion syndromes—and these additional results were sometimes available only on an opt-in basis, and/or at extra cost. In our sample only one IC did not include any mention of screened conditions. However, while nearly all IC listed the conditions screened, only about half (n=17) included any phenotypic descriptions of any of the conditions, and very few included any contextual information about quality of life (see Table 3). Phenotypic descriptions, when they did appear, were usually very brief,

general, and symptom-focused. For example, an IC for the verifi™ test included this description:

Trisomy 21, trisomy 18, and trisomy 13 are three of the most commonly occurring trisomies seen in babies at birth. Although the outcomes are variable, these conditions can cause mild to severe intellectual disabilities, and can cause multiple physical problems including congenital heart defects, defects in other organs, and a shortened life span.

An IC from the Oregon Health Authority included this description of the same conditions:

Down syndrome: children with Down syndrome have a wide spectrum of physical and cognitive disabilities.

Trisomy 18: children with trisomy 18 have significant physical and cognitive disabilities. Their life expectancy is shortened.

Trisomy 13: children with trisomy 13 have significant physical and cognitive disabilities. Their life expectancy is shortened.

While both documents included a web address for further information, these descriptions by themselves offer minimal phenotypic information. For other aneuploidies and microdeletion syndromes, phenotypic descriptions were even rarer.

A few IC did include more detailed information, including information about quality of life for children born with a screened condition. A patient information booklet from Intermountain Healthcare included this description of Turner syndrome (45,X):

Girls with Turner syndrome may be born with heart defects requiring surgery, and generally they are short compared to their family members. They may have learning disabilities, but most girls with Turner syndrome have normal intelligence. When a woman is pregnant with a girl with Turner syndrome, the pregnancy has a very high chance of ending in miscarriage.

A description of Turner syndrome from an IC for the Panorama™ test included this information:

Girls with Monosomy X are shorter than average. Some girls have heart or kidney defects, hearing problems, and some have minor learning disabilities. Girls with Monosomy X may need growth hormone treatments in early childhood and usually need sex hormone treatments at the time of puberty. As adults, they often have infertility.

This level of detail about potential phenotypes for screened conditions was uncommon in the sample.

Information about test counseling and psychosocial issues

Most IC (n=23) noted that patients should think about or discuss any questions prior to deciding about cfDNA screening, and many of these (n=15) specifically mentioned pre-test genetic counseling (see Table 4). For example, an IC for the Harmony™ test noted, “Talk to your healthcare provider before you decide if the Harmony Prenatal Test is appropriate for

you,” and just before the patient signature line stated, “I have had the opportunity to discuss the purposes and possible risks of this testing with my doctor or someone my doctor has designated. I know that genetic counseling is available to me before and after the testing.” An IC from Women’s Health Partners, LLC (an obstetrics and gynecology practice in Florida, US) included the following statements:

Genetic counseling is recommended to all pregnant women who will be 35 years old or older at delivery and is available to all pregnant women. ... Genetic Counseling with a certified genetic counselor is available to all patients at Women’s Health Partners. Please discuss these options with your physician or midwife.

The cost to the patient (if any) of either pre- or post-test counseling was not mentioned in any IC. Over half of all IC recommended or suggested post-test genetic counseling (as noted above), but few mentioned psychosocial considerations or other supports. For example, two IC mentioned that prenatal screening can cause anxiety for patients, and two IC mentioned that patients may make termination decisions based on the results of screening and testing. Only one IC mentioned any support groups that are available for families affected by a genetic condition.

Information about other test considerations

Although over one-third of IC (n=13) indicated that the patient was responsible for the cost of cfDNA screening (either through insurance or out-of-pocket), only five IC (as noted above) listed the cost of the test (see Table 4). Over half of IC (n=18) explained test procedures involving the patient, which consist solely of a blood draw (and, in case of assay failure, a second blood draw). As noted above, many IC discussed sample retention; however, less than one-third of IC (n=9) disclosed that the patient’s health care provider may share information about her pregnancy outcome with the testing laboratory (commonly done for evaluating test performance). While (as noted above) IC frequently mentioned regulatory approval of laboratory facilities (e.g., CLIA (Clinical Laboratory Improvement Amendment) validation in the US), only three IC mentioned whether the test was subject to and/or had received regulatory approval; all of these referenced the fact that cfDNA screening has not received approval from the US Food & Drug Administration (although such approval is not currently required). (See Table 4.)

Discussion

This analysis of 32 IC revealed a wide range in the quantity and quality of information offered to women at the time of their decision-making about cfDNA screening. Commercial IC and Non-Commercial IC differed most strikingly in their length and reading difficulty, which appeared to stem from a greater tendency among Commercial IC to combine legal disclosures, financial responsibility statements, and informed consent information into one document. Such documents contained a great deal of useful information, but were sometimes visually crowded and linguistically complex. Readability of IC is crucial if these documents are to be useful for women making decisions about prenatal screening; in the US, for example, over three-quarters of women of childbearing age do not have a college degree, and education levels vary greatly between populations from different backgrounds (46).

Indeed, US federal guidelines for labeling of medical devices specify that information directed at patients should be at an eighth-grade reading level or below (47). We suggest that readability of IC was also compromised by combining IC with laboratory order forms, examples of which we found in both Commercial and Non-Commercial IC. Such forms often crowded clinician- and patient-directed information together into a single sheet, using small fonts and very little empty space. Information and questions directed at clinicians, such as medical billing codes and clinical indications for testing, contain jargon and abbreviations that may confuse patients, and interspersing these elements with information directed at patients can further confound efforts to communicate clearly and facilitate informed decision-making.

Information about the test itself varied greatly within our sample set of IC. For example, while most IC recommended confirmatory diagnostic testing for screen-positive results and some IC strongly emphasized that cfDNA screening is not diagnostic, nearly a quarter of IC never used the phrases “not diagnostic,” “screen,” or “screening test” to describe cfDNA screening. Explanations that cfDNA is not diagnostic are particularly important, given reports that many women misunderstand cfDNA screening results to be diagnostic and may even terminate without confirmatory testing (37, 48). Such misunderstandings might also be lessened by clear expectations regarding screening results, but many IC in our sample did not explain how results would be presented, to whom they would be provided, and/or that results can be incorrect. The high test sensitivity of cfDNA screening was often cited by IC in our sample (most often mentioned was the 99% sensitivity for trisomy 21 in high-risk pregnancies); but to understand the chance that an actual screening result will be correct, sensitivity is less helpful than positive and negative predictive value (PPV and NPV)—which were not mentioned in any IC in our sample. In addition, only a few IC discussed genetic information that cfDNA screening can reveal about a parent, information that may take many patients by surprise. Many patients and clinicians alike were surprised to hear news reports that cfDNA screening may reveal tumors or cancer in the pregnant woman, information that was not included in any IC in our sample; though these reports were published after the documents in our sample were collected, multiple laboratories had for some time been aware of this capability and were collecting data (and sometimes returning information to clinicians) about this phenomenon (49). Overall, though many IC mentioned the benefits of cfDNA screening, few discussed these informational risks, and information about psychosocial issues—such as anxiety or termination decision-making—was notably absent from nearly all IC.

Finally, information about screened conditions was sparse in our sample and rarely included information about phenotypes, variability, or quality of life. While truly complete information about screened conditions is impractical and likely unnecessary in pre-test decision-making, even brief descriptions of screened conditions may provide contextual information that conveys information beyond descriptions of genetic mutations and helps patients understand the diversity of conditions being screened. One way to offer interested patients more information without overwhelming others is to list other resources; however, although many IC included links to company or clinic websites with more information (which we did not assess in this study), only one IC listed any patient support organizations

for genetic conditions—resources that many families value for the depth and relevance of condition-specific information they can provide (33, 50).

Based on our findings, along with prior recommendations for clinical informed consent and best practices for cfDNA screening, below we offer recommendations for facilitating informed decision-making for cfDNA screening with written informed consent documents.

Recommendations

1. Informed consent should be sought before performing cfDNA screening, and should be preceded by pretest counseling. Written informed consent is a good option, but written and/or signed documents do not eliminate the need for verbal counseling.
2. Informed consent documents should be visually separate from laboratory order forms, legal agreements, and financial responsibility statements, and should include a copy that the patient can take home.
3. Informed consent documents should be easy to read. Plain language should be used preferably written at a 9th grade reading level or below in the patient's native language. Type size should be large enough for ease of reading, with plenty of "white space" on the page, and text should never or very rarely be in all-capital letters or italics.
4. Informed consent documents should clearly state the benefits and risks of cfDNA screening, including unexpected findings, psychosocial considerations, and the potential for decision-making about pregnancy continuation and/or management. Alternatives to cfDNA screening should be presented, including the option to decline all prenatal screening/testing for fetal conditions.
5. Any clinical indications for offering cfDNA screening (e.g., elevated risk from prior screening), along with test cost and/or coverage considerations, should be explained verbally and/or in writing.
6. Informed consent documents should clearly state that cfDNA is not diagnostic, that there can be false positives, errors, and assay failures, and that any screen-positive results should be confirmed with diagnostic testing. Statistics regarding the test, if given, should include false-positive rates, positive predictive values, or other numerical indicators that clarify how often screening results are correct or incorrect.
7. Informed consent documents should recommend genetic counseling for screen-positive results, and the availability (and potential cost) of pre-test and post-test genetic counseling for any patient should be disclosed.
8. Informed consent documents should list all conditions being screened, and should include a brief, family-relevant explanation of the conditions (e.g., possible phenotypes, quality of life) and variability within and between

them. Identifying patient support organizations for screened conditions is also helpful, if space allows.

9. Regardless of whether a signature is required, informed consent documents should include a simple consent statement, not combined with legal or financial agreements. Also prominently listed should be the name and contact information of a local clinical provider who is available for further questions.

Limitations

Documents were collected for this analysis during a limited time period ending in December 2014. Due to the rapid changes in cfDNA screening tests and in professional recommendations for offering cfDNA screening, IC offered by any particular laboratory or clinic may have changed since our sample set was collected. While every effort was made to represent the range of IC available to patients, this sample is not comprehensive; nor is it weighted to represent proportionate audiences for particular documents, as we did not have data to support such weighting. For example, documents used only by one clinical practice were not weighted differently than documents distributed by a commercial laboratory for use by many clinics. Many documents in our coding set included links or references to websites, online pamphlets, or other educational materials, while others may be physically distributed with additional printed materials; as assessing the availability and distribution of these additional materials was beyond the scope of this study, such other materials were not sought out or analyzed. Finally, this analysis cannot assess the content or impact of verbal counseling or other decisional support that patients may receive before choosing or refusing cfDNA screening, or after receiving results. We emphatically affirm the value of such counseling and support, and recognize that informed decision-making is a process that is documented—but never fully encapsulated—in reading and signing a form.

Conclusion

The availability of informed consent documentation from many health care providers and commercial laboratories points toward progress in assuring informed decision-making regarding cfDNA screening. However, the variable quality of these documents suggests the need for informed consent guidelines to support laboratories and clinics. Toward this end, we have offered recommendations for written materials to guide and document informed consent before performing cfDNA screening. In combination with verbal counseling by a health care provider, informed consent documents that follow these recommendations can help ensure that pregnant women and their families have the opportunity to make informed, values-appropriate decisions about cfDNA screening.

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Figure 1.
Source of final coding set IC by country

Table 1

Informed consent documents (IC)

	IC solicited from professional contacts	IC collected from Internet searches	IC solicited from genetic counseling online mailing list	Total IC
Initial sample	21	69	3	93
Final coding set	5	24	3	32

Table 2

Commercial IC versus Non-Commercial IC

	Commercial IC (n=22)	Non-Commercial IC (n=10)	All IC (n=32)
Median word count (Range)	944 (214–2132)	540 (361–1567)	814 (214–2132)
Median Flesch-Kincaid reading grade level (Range)	12.0 (8.9–13.8)	10.6 (8.6–11.7)	11.5 (8.6–13.8)
Mentioned regulatory approval of laboratory facilities	13 (59%)	0 (0%)	13 (41%)
Mentioned or discussed sample retention or use	19 (86%)	1 (10%)	20 (63%)
Cited the sensitivity of cfDNA screening for any condition	10 (46%)	3 (30%)	13 (41%)
Mentioned limitations on cfDNA screening (e.g., multiple gestations, bone marrow transplant recipients)	17 (77%)	3 (30%)	20 (63%)
Clearly stated that cfDNA screening is optional, or that patient can refuse	10 (46%)	3 (30%)	13 (41%)
Mentioned the option of post-test genetic counseling	15 (68%)	4 (40%)	19 (59%)
Stated the cost of cfDNA screening	1 (5%)	4 (40%)	5 (16%)
Mentioned the possibility of assay failure	12 (55%)	7 (70%)	19 (59%)

Table 3

Information about test capabilities, results, and screened conditions

	Number (%) Total n=32
Used the phrase “not diagnostic” to describe cfDNA screening	15 (47%)
Used the phrase “screen” or “screening test” to describe cfDNA screening	19 (59%)
Used “not diagnostic” AND/OR “screen” phrases	25 (78%)
Mentioned alternative tests (including screening and diagnostic testing)	10 (31%)
Described alternative tests (including screening and diagnostic testing)	5 (16%)
Noted gestational age when cfDNA screening can be offered	24 (75%)
Mentioned format of test results (e.g., risk score or “Aneuploidy detected”)	19 (59%)
Stated person to whom test results are returned	16 (50%)
Recommended confirmatory diagnosis for screen-positive results	28 (88%)
Noted that results can be incorrect (including false positives/negatives)	23 (72%)
Test sensitivity listed	13 (41%)
Test specificity listed	8 (25%)
Positive predictive value (PPV) listed	0 (0%)
Negative predictive value (NPV) listed	0 (0%)
Mentioned that cfDNA can reveal genetic anomalies in a parent	4 (13%)
Mentioned that cfDNA can reveal tumors or cancer in the mother	0 (0%)
Listed at least one screened condition	31 (97%)
Included phenotypic description of trisomies 21, 18, and/or 13	17 (53%)
Included phenotypic description of any other condition	9 (28%)

Table 4

Information about counseling, psychosocial issues, and other considerations

	Number (%) Total n=32
Directed patients to think about or discuss questions prior to screening	23 (72%)
Mentioned availability of pre-test counseling	15 (47%)
Mentioned cost (if any) of genetic counseling	0 (0%)
Noted that prenatal screening can cause anxiety	2 (6%)
Noted that results may lead to decision-making about termination	2 (6%)
Listed any support groups for families with a genetic condition	1 (3%)
Mentioned that patient is responsible for cost of cfDNA screening	13 (41%)
Stated the cost of cfDNA screening	5 (16%)
Described test procedures involving the patient	18 (56%)
Disclosed that pregnancy outcomes may be shared with the laboratory	9 (28%)
Mentioned regulatory oversight of cfDNA screening	3 (9%)