Next-Gen Informed Consent for Prenatal Testing

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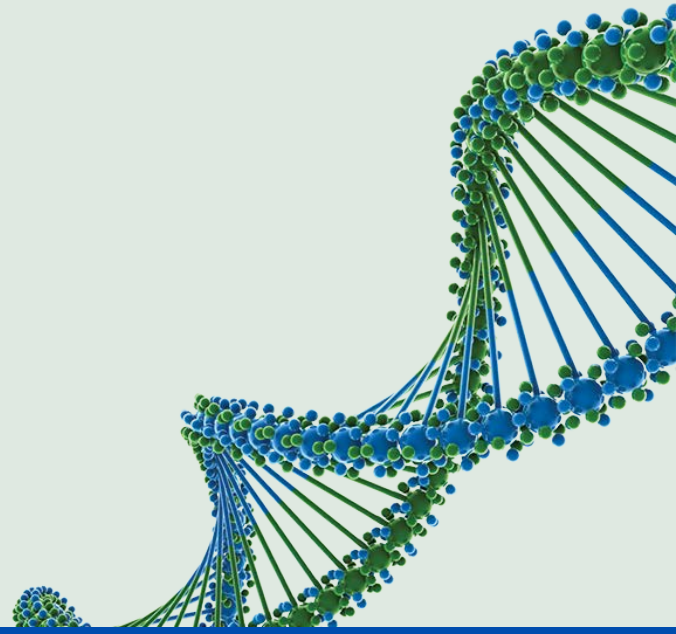


Disclosure

- 2009-2012

  RNA study to determine Down syndrome risk

  Funding Agency: Sequenom

  Role: Clinical Site Director

  2013- present

  "DNA First: Primary screening for Down syndrome by Maternal plasma DNA"

  (Palomaki PI)

  Funding Agency: Natera

  Role: Clinical Site Director

- 2012- present: Speaker Bureau, Sequenom, CMM

Objectives

- Define informed consent
- Discuss the challenges and complexities of obtaining informed consent in the era of advancing genetic technology
- Review potential approaches to the informed consent process that can meet the needs of all stakeholders

Background

- ccfDNA testing for common aneuploidies has been in clinical practice since 2011
- Palomaki et al published the first clinical validation study showing a very high detection rate and a low false positive rate for Down Syndrome
- Since then the possibilities/utility of ccfDNA have exploded

How good is ccfDNA? Why are the fuss?

- Detection rate for Down Syndrome is about 98%
  - "98 of 100 Down syndrome fetuses tested will have a positive result; one will be missed and another will be a no-call."
- False positive rate is about 0.2% or less

  "Only 1 in 500 normal fetuses will have a positive DNA test for Down syndrome."
- Failure/No call rates ranges from 1% to 5%

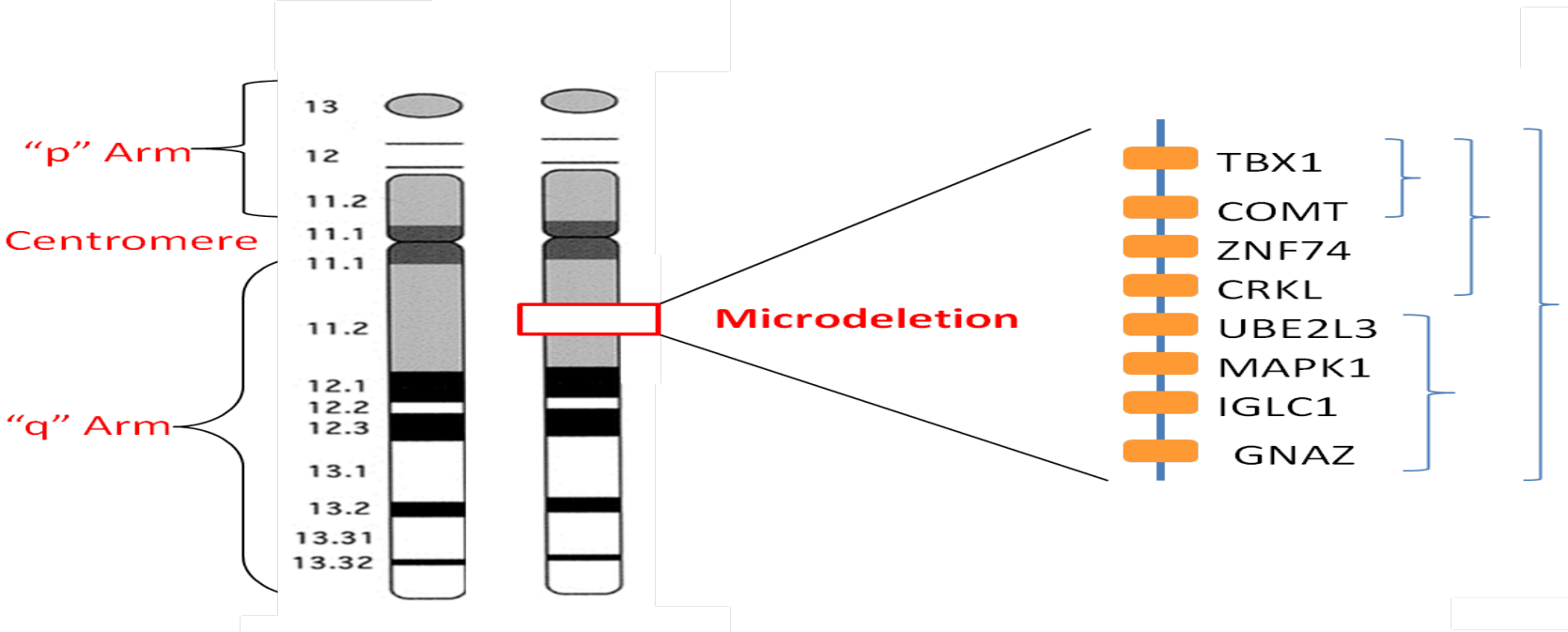
  "Depending on the test, between 1 and 5 of every 100 women will have a test result that does not provide useful information about the woman's Down syndrome risk"

Expanded Screening

- Fetal sex
- Sex Chromosomal Aneuploidies
- Microdeletions
  - 22q11.2
  - 1p36 deletion
  - Angelman
  - Prader-Willi
  - Cri-du-chat
- Trisomies 16, 22

What is a microdeletion?

- 1MB (megabase) = 1 million base pairs
- The 21st chromosome is about 50 MB
- Microdeletions are 100kb to several MB
- Karyotypes can usually only visually detect deletions ≥7-10 MB



Phenotype will depend on the size of the deletion & the genes involved.

Why screen for microdeletions?

- May result in physical and/or intellectual impairments that can be more severe than whole chromosomal abnormalities

What is Informed Consent?

- Definition:
  - Consent to surgery by a patient or to participation in a medical experiment by a subject after achieving an understanding of what is involved
  - First Use Circa 1957
    - » Websters Dictionary

What is informed consent?

- Important to make the patient aware of the benefits and harms that may occur as a consequence of the testing process
  - Schrijver et al, 2012
- Embedded in the ethics of autonomy
  - An individual's right to self-determination
- Advances in technology increasingly facilitate parental choice with regard to prenatal diagnosis
  - Chitty et al, 2014

Informed Consent

- Central to clinical genetic counseling process
  - Reviews:
    - » purpose, benefits and limitations of a given test
  - Enables:
    - » patients to ask questions or raise concerns prior to test
  - Protects
    - » All stakeholders?
    - » Certaintly the health care provider

Why are we addressing this topic ?

- World of genetic technology has explode
- In the past, one or at most a few genetic tests were ordered at once
- Genetic testing has shifted towards a multiplexed approach
  - Microarrays
  - Non-invasive prenatal testing (NIPT)
  - Next generation sequencing
  - Carrier panels
- New ways of offering tests are coming
  - Direct to consumer

Why are we addressing this topic ?

- Requires different approach(es) to informed consent from perspective of all stakeholders
  - Patient
  - Physician
  - Providers of genetic test (laboratories)

Difficult Issues Encountered in the Informed Consent Process

- New error in genetics
- Need to discuss potential benefits and risks of testing
- Prenatal testing may also identify an underlying condition in the mother
  - Seen prior to NIPT with carrier screening, particularly CF, though also Gaucher disease and others
- Now with NIPT:
  - sex chromosome aneuploidies in women with no phenotype are being identified
- NIPT also has the potential to reveal undiagnosed malignancy

Let's start with something simple…Determining Fetal Sex

- Cell free DNA testing for fetal sex has been (is?) offered as a stand-alone test
- Usually determined by identifying sequences or SNPs from the Y-chromosome in the cell free DNA
- Highly reliable (99% accurate), but not perfect
  - Sufficient cell free DNA must be available; usually performed at 10 weeks' gestation or later
  - Could be confused by vanished twin (although a female fetus is present, some placenta from the vanished male twin may remain)

Ethics of Offering Fetal Sex

- Reporting of fetal sex banned in some countries (China)
- Commonplace and valued by patients in the US (via ultrasound, results of karyotype)

Models of Informed Consent

- Detailed education process
  - Review the purpose, benefits, and limitations of a genetic test
  - Is this traditional model sustainable?
    - Time?
    - Number of genetic counselors?
    - Reimbursement?
    - Resources?

What is the model of informed consent presently?

- Is there a uniformity in the way that we consent for prenatal tests
  - No
  - Varies on health care provider
    - » Style
    - » Time
    - » Knowledge?

What is the model of informed consent presently?

- Should the model of informed consent vary based on the type of test that we order?
  - NIPT
  - Karyotype
  - single gene disorder testing
  - genome wide analysis with microarray
  - Karyotype
  - whole exome/genome sequencing as that is likely in the future of prenatal genetics.

Is this the best model and if so for who?

- **Stakeholders:**
- (1)Patient:
  - At first glance yes
    - However, if an enormous time is taken away from other crucial items to discuss, then no
- (2) Health care provider:
  - Uncertain
- (3) Laboratory:
  - Uncertain

What is the “best” model of informed consent?

- Ideally:
  - Individualized approach to each family is required to ensure autonomous choice and informed consent regarding prenatal diagnostic testing within the local ethical and legal framework
    - » Skirton et al,

      European Journal of Human Genetics (2014)

Is this practical?

- Time?
- Money?
- Other resources..
  - Genetic counselors

What is the best model for informed consent?

- Current practice
  - First we need to define what current practice is.
  - Variable?
- Improved education with mandated pretest and posttest counseling as suggested by ISPD, ACOG, SMFM
  - Would require more education for practitioners ordering these tests if pretest and post-test counseling is not going to be done by genetic counselors

How will we do this? What are the possibilities?

- Patient Education via:
  - in- office video education
  - home video education
  - Podcasts
- Physician Education
  - Traditional learning
  - Video learning
  - MOC

What are some potential models for informed consent for NIPT?

- Verbal informed consent
  - as we do now for integrated testing
  - However, with NIPT, we must talk about no calls, and potential findings in both mother and baby that are unexpected
- For expanded screening:
  - Group the disorders into “severity” of diseases and obtain informed consent for groups of diseases
  - Laboratory can provide a written script to the health care provider that can aid them
- Traditional written informed consent

Can we take advantage of Social Media?

- Many of our patients have/use smartphones
  - Can we have them go to our hospital (or society?) Facebook pages
    - » listen to podcast about the genetic testing
    - » Informed consent could merely be that verbal or written statement that they listened to the podcast
  - Could develop an “app” about different genetic testing options