# Genetics 101 for BRCA and Non-Invasive Prenatal Testing:

Presented by: Steven Keiles, MS, LCGC Director, Genetic Counselor Organization

September 28, 2015

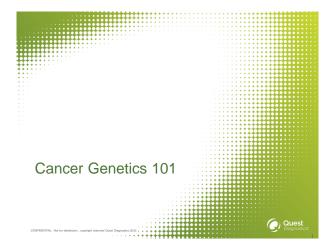


### **Presentation Agenda**

- Cancer Genetics 101
- "Red Flags" for hereditary cancer
- BRCA1 and BRCA2 genes
  - · Cancer risks, testing criteria, and management guidelines
- Additional hereditary breast cancer genes
  - · Cancer risks, testing criteria, and management guidelines
- Noninvasive prenatal screening (NIPS)
- Chromosomal abnormalities
- Evolution of prenatal screening
- Clinical utility of NIPS
- Genomic Client Services

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### How Does Cancer Develop?

- Sporadic cancer
  - Sporadic cancer develops due to genetic changes within the cells of a specific body tissue
  - Causes for sporadic cancer include aging, hormone history, radiation exposure, smoking, alcohol use, BMI

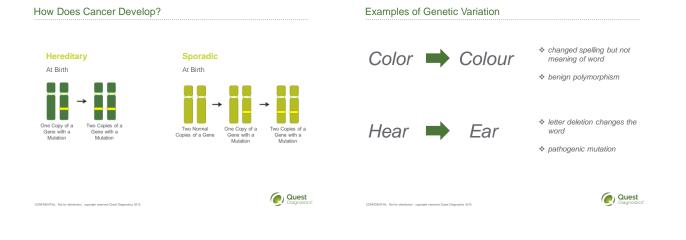
### Most contributing factors are still unknown

Hereditary cancer

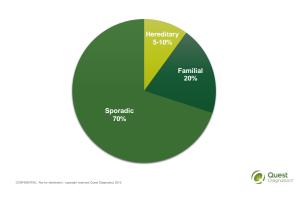
- · Hereditary cancer results from a mutation in a gene
- Gene mutations can be passed down in families, causing an increased susceptibility to cancer
- All cancer is genetic, but most cancers are not hereditary

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What Percentage of Cancer is Hereditary?

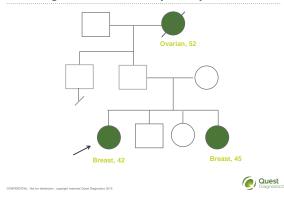


### "Red Flags" for Inherited Susceptibility to Cancer

- Cancer in 2 or more closely related relatives
- Multiple generations affected
- Early age at diagnosis
- Multiple primary tumors
- · Bilateral or rare cancers
- Constellation of tumors consistent with a specific cancer syndrome
- Certain ethnic backgrounds (e.g. Ashkenazi Jewish ancestry)



2



## Assessing Your Patient's Family History

# Genetic Testing Strategy

### • The right person

 When possible, testing should begin with the individual most likely to test positive (family member who has actually had cancer, youngest age at diagnosis, bilateral disease, multiple primary cancers)

### • The right test

- Consider:
  - Is there a known familial mutation?
  - Is the patient of Ashkenazi Jewish ancestry?
  - What types of cancers have been diagnosed in the patient and/or the family?
- Single gene(s) vs targeted panel vs large panel

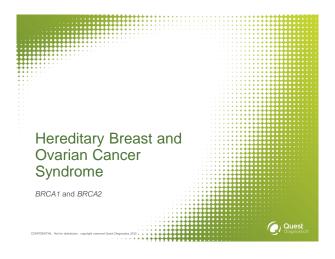
### • The right time

- Are the test results needed for surgical decision making?
- Consider the psychosocial implications of genetic testing

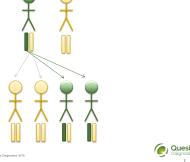
• Testing is generally not warranted for individuals under the age of 18

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# Autosomal Dominant Inheritance



# BRCA1 and BRCA2

### The most common high-risk hereditary breast cancer genes

- Autosomal dominant
- Carrier frequency ~1/400 in general population
- Carrier frequency ~1/40 in Ashkenazi Jewish population

### Cancer Risks to age 70

|                      | BRCA1      | BRCA2      |
|----------------------|------------|------------|
| Female Breast Cancer | 55% to 65% | 45% to 47% |
| Ovarian Cancer       | 39%        | 11% to 17% |
| Male Breast Cancer   | 1.2%       | 6.8%       |

\*Also, increased risks for prostate cancer, melanoma, and pancreatic cancer

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### Medical Management Guidelines: BRCA positive

| Cancer     | Intervention    | Age and Frequency   |
|------------|-----------------|---|
| Breast     | Screening       | Clinical breast exam every 6-12 months, starting at age 25 y for women and 35 y for men<br>Annual breast MRI, starting at age 25 y for women, add annual mammogram at age 30; consider baseline mammogram at 40 y for men |
|            | Chemoprevention | (i.e. Tamoxifen, Raloxifene, aromatase inhibitors)  |
|            | Surgery         | Discuss risk-reducing mastectomy  |
| Ovarian    | Surgery         | Risk-reducing bilateral salpingo-cophorectomy, ideally between the ages of 35 and 40 $\ensuremath{y}$   |
|            | Chemoprevention | (i.e. oral contraceptives)  |
|            | Screening       | Transvaginal ultrasound and CA-125 blood test; repeat every 6 months starting at age 30-35 $y^{\ast}$   |
| Prostate   | Screening       | Starting at age 40 y for BRCA2 carriers / consider for BRCA1 carriers   |
| Melanoma   | Screening       | No specific guidelines: Consider annual dermatological examinations   |
| Pancreatic | Screening       | No specific guidelines: Consider pancreatic cancer screening if + family<br>history   |

\*Ovarian cancer screening has not been shown to be sufficiently sensitive or specific to support routine screening recommendation but can be considered at the clinician's discretion



### Testing Criteria for BRCA1 and BRCA2

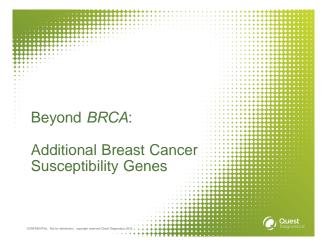
| Family History of Breast Cancer  | Personal His                   | story of Breast Cancer*   |
|--|--------------------------------|---|
| <ul> <li>Relative with a previously<br/>identified BRCA1 or BRCA2</li> </ul>   | Age at<br>Diagnosis            | Additional Criteria<br>Only 1 of the following is necessary.  |
| mutation   | s45 y                          | <ul> <li>No additional criteria necessary</li> </ul>  |
| <ul> <li>1st/2nd-degree blood relative<br/>who meets any criteria in<br/>the Personal History sections</li> </ul>  | ≤50 y                          | <ul> <li>&gt;2 primary breast tumors"</li> <li>&gt;1 close blood relative' with breast cancer</li> <li>Limited family history</li> </ul>                                  |
| <ul> <li>3rd-degree relative with breast<sup>a</sup><br/>and/or ovarian<sup>b</sup> cancer and<br/>&gt;2 close blood relatives<sup>c</sup> with</li> </ul> | ≤60 y                          | Breast cancer that is negative for ER, PR, and HER2<br>(triple negative)  |
| breast and/or ovarian <sup>b</sup> cancer  |                                | Patient is male   |
| Personal History of Other<br>(Nonbreast) Cancers   |                                | <ul> <li>≥1 close blood relative<sup>c</sup> with breast cancer<br/>diagnosed by age 50 or with epithelial ovarian<sup>b</sup><br/>cancer diagnosed at any age</li> </ul> |
| Epithelial ovarian cancer*   | Any age                        | <ul> <li>≥2 close blood relatives<sup>c</sup> with breast cancer</li> </ul>   |
| Pancreatic or prostate cancer     with >2 <sup>d</sup> close blood relatives <sup>c</sup>  | Anyage                         | <ul> <li>≥2 close blood relatives<sup>c</sup> with prostate cancer<br/>(Gleason score ≥7) or pancreatic cancer</li> </ul>   |
| diagnosed with breast, ovarian. <sup>b</sup>   |                                | <ul> <li>≥1 close male blood relative<sup>c</sup> with breast cancer</li> </ul>   |
| pancreatic, or prostate cancer<br>(Gleason score ≥7)   | pancreatic, or prostate cancer | <ul> <li>Ethnicity (eg. Ashkenazi Jewish) associated with<br/>higher mutation frequency</li> </ul>  |



Genetic Testing Strategy – BRCA1/BRCA2

### BRCAvantage™, Comprehensive (includes large rearrangements)

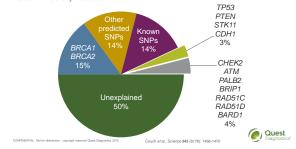




Beyond BRCA: Other genes

Mutations in *BRCA1* and *BRCA2* explain 15%-20% of hereditary breast cancer cases

Mutations in TP53, PTEN, STK11, CDH1, and PALB2 explain an additional 3% - 4.5% of hereditary breast cancer



### Beyond BRCA: Gene Panels

### BRCAvantage Plus™

BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, PALB2

- Simultaneous analysis of seven genes associated with hereditary breast and other cancers
- These genes all have NCCN guidelines for medical management if results are positive
- More efficient and cost-effective if personal/family history raises concern for more than one syndrome
- May be useful for those who have previously tested negative for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility
- Also available as a reflex test if BRCA analysis is negative

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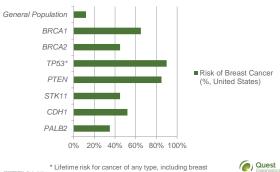
### BRCAvantage Plus™

|                   | Gene  |       |      |      |      |       |       |
|-------------------|-------|-------|------|------|------|-------|-------|
| Associated Cancer | BRCA1 | BRCA2 | TP53 | PTEN | CDH1 | STK11 | PALB2 |
| Breast            |       |       | •    |      | •    | •     |       |
| Colorectal        |       |       | •    |      | •    |       |       |
| Endometrial       |       |       |      |      |      |       |       |
| Stomach           |       |       |      |      |      |       |       |
| Melanoma          |       |       |      |      |      |       |       |
| Ovarian           |       |       |      |      |      |       |       |
| Pancreatic        |       |       |      |      |      |       |       |
| Prostate          |       |       |      |      |      |       |       |
| Other             |       |       | •    | •    |      | •     |       |

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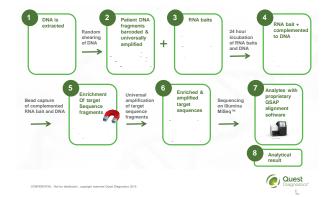


### Breast Cancer Risks



### Genetic Testing Criteria and Management Guidelines

| Gene        | Genetic Testing Criteria   | Management Guidelines  |
|-------------|----------------------------|--|
| BRCA1/BRCA2 |                            |  |
| TP53        | NCCN: Genetic/Familial Hig | h-Risk Assessment: Breast and Ovarian  |
| PTEN        |                            |  |
| CDH1        | NCCN Clinical Practice Gu  | idelines in Oncology: Gastric Cancer   |
| STK11       | None (Clinical Diagnosis)  | NCCN: Genetic/Familial High-Risk<br>Assessment: Colorectal   |
| PALB2       | None                       | ACS recommends screening with MRI for<br>women with at least 20% lifetime risk of<br>breast cancer |
|             |                            | Quest  |



BRCAvantage Plus™ Technology

# Interpreting Results of Genetic Tests

- · Interpretation Summary
- Color-Coded 5-Tier Classification Known Pathogenic (RED)
  - Likely Pathogenic (RED)
  - VUS (YELLOW)
  - Likely Benign (not reported)
- No Mutation Detected (GREEN)
- Comprehensive Interpretation
- · ACMG Guidelines

| Contraction of the second              |   |   |
|--|---|---|
| Gender F<br>Press NG<br>Patient ID, NG | Reprinter DBD10007C_002587<br>Reprinter: 0021312<br>Collocati 00252004<br>Reprint 00252004 / 0000 PDT<br>Reported 00252004 / 0000 PDT | Class F 1930340 1234547<br>COLDENAL ANTERIO<br>TEST CLEMPT SNARD<br>Any TEST DEPARTMENT<br>1395 S COLLEGEVELLE RD<br>COLLEGEVELLE, PA 19428 |
| BRCAVANTAGE/T                          | MI PLUS (BRCA1, BRCA2, TPS3, PTE  | E CON1. STK11. PALB21   |
| INTERPRETATION SUMMARY                 |   | Lite  |
| POSITIVE FOR A KNOWN PATHOD            | INC MUTATION  |   |
| BRCALQ PESUL75                         |   | Leb E   |
| Test Performed                         | Result  | Interpretation  |
| ERCAT Sequencing                       | <.34564C  | KNOWN/PA/HOGINE   |
| BRCA1 Del/Dup                          | NEWTON  | NO M/TRTICH DETRICTIO   |
| BRCA2 Sequencing                       | NEGRATIVE   | NO MUTATION DETECTED  |
| BRCA2 Del/Dup                          | NCG47WC   | NO MUTATION DETECTED  |
| 1912 86544.75                          |   | Lab. B  |
| Test Performed                         | Result  | Interpretation  |
| 1953 Sequencing                        | NEGATIVE  | NO MUTATION DETECTED  |
| 1953 Del Dup                           | NUSATIVE  | NO-MUTATION DETECTED  |
| \$7611 9656675                         |   | Let 6   |
| Test Performed                         | Real  | Interpretation  |
| STK11 Sequencing                       | NIGATIVE  | NO MUTATION DETECTED  |
| ETK11 DelDup                           | NEGATIVE  | NO MUTATION DETECTED  |
| PTEN RESULTS                           |   | Leb: 6  |
| Test Performed                         | Result  | Interpretation  |
| PTEN Sequencing                        | NEGATIVE  | NO MUTATION DETECTED  |
| PTEN Del/Dup                           | NEGATIVE  | NO MUTATION DETECTED  |
| CONT RESATS                            |   | Let: 0  |
| Test Performed                         | Real  | Interpretation  |
| CONT Sequencing                        | NDGATIVE  | NO MUTATION DETECTED  |
| CEHI Ov/Dup                            | NEGATIVE  | NO MUTATION DETECTED  |
| PHURP PERSON                           |   | Let 6   |
| Test Performed                         | Result  | Interpretation  |
| PAL83 Sequencing                       | NIGATIVE  | NO-MUTATION DETECTED  |
| CLIENT MEMORY                          | SPECTATIN DECOMPT_A02507  | PAGE 1 0F 3   |

### Possible Test Results

# POSITIVE (Pathogenic, Likely Pathogenic):

- Refer to NCCN Management GuidelinesRelatives should consider single-site testing
- NEGATIVE
- Uninformative result versus true negative. True negative only if family history is due to a known mutation.
- Consider additional testing for your patient and/or other family members

### VARIANT OF UNCERTAIN SIGNIFICANCE:

- Additional data required for interpretation (e.g., family studies, functional studies)
- Patient recommended to check in with MD/Quest Diagnostics on regular basis (e.g., every year) as variant status may change
- Management based on patient's personal and family history
  CONTENTION. No to debuter, capacity represend care demonstra 2015

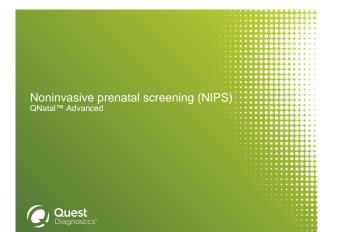




- · Co-founded by Quest Diagnostics and Inserm
- Provides scientists and commercial laboratories around the world open access
  to BRCA1 and BRCA2 genetic data
- The goal of BRCA Share is to accelerate research on BRCA gene mutations
   and clarify the pathogenicity of variants of uncertain significance

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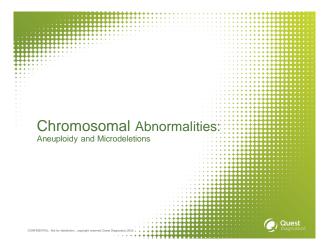




- Overview
  - Quest Diagnostics
  - Chromosomal abnormalities
  - · Evolution of prenatal screening
  - Clinical utility of NIPS
- Performance of QNatal Advanced
- Summary

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### Chromosomal Aneuploidy

| • | Common | autosome |  |
|---|--------|----------|--|
|   |        |          |  |

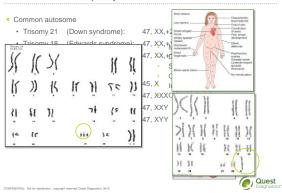
- Trisomy 21 (Down syndrome): 47, XX,+21
- Trisomy 18 (Edwards syndrome): 47, XX,+18 47, XX,+13 • Trisomy 13 (Patau syndrome):

Common sex chromosome

- Monosomy X (Turner syndrome): 45, X
- Triple X (Triple X syndrome): 47, XXX Klinefelter (Klinefelter syndrome): 47, XXY
- XYY 47, XYY
- (XYY syndrome):



### Chromosomal Aneuploidy: Clinical Picture



### **Chromosomal Microdeletions**

- Microdeletion: a chromosomal deletion too small to be detected by standard cytogenetic analysis
- Microdeletion syndrome Characteristics vary based on the size and location of the deletion 22q

1р

15a

- DiGeorge syndrome:
- 1p36 syndrome:
- Angelman syndrome:
- · Prader-Willi syndrome: 15q
- · Cri-du-chat syndrome: 5p
- Wolf-Hirschhorn syndrome: 4p
- · Jacobsen syndrome: 11a
- Langer-Giedion syndrome: 8q



### Chromosomal Microdeletions: Clinical Picture

- Microdeletion: a chromosomal deletion too small to be detected by standard cytogenetic analysis
- Microdeletion syndrome Characteristics vary based on the size and location of the deletion
  - DiGeorge syndrome: 22q
  - 1p36 s@raddomocedefect 1p
  - · AngelnSahizyndhonnie
  - 15q
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   Criticut Bankows Delay 15q
   Criticut Bankows Charles Delay 15q
   Criticut Bankows Charles Delay 15p
   Wolf-Higher Markows Charles Delay 15p
   Academic State Bankows Charles Delay 11q
   Langer Gileffield syndrome: 8q

- - HyperphagiaObesity

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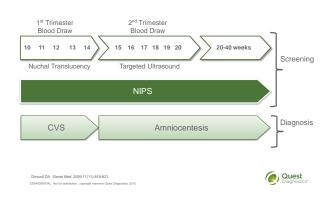


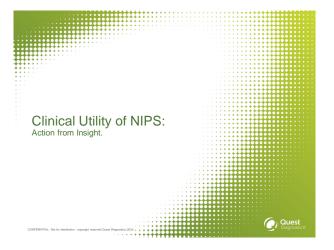


### Evolution of Fetal Aneuploidy Screening

| • | •••••  |                    |                |   |  |
|---|--|--------------------|----------------|---|--|
| <u>1960s</u>                            | <u>1980s</u>   | 1988               | <u>1996</u>    | <u>1997</u>   | 2011   |
| Maternal<br>Age                         | MSAFP  | > Triple<br>Screen | Quad<br>Screen | Integrated<br>Screen +  |  |
| Detection (S                            | ensitivity) Rate   | e (%)              |                |   |  |
| 27                                      | 36   | 60 - 74            | 70 - 81        | 80 - 95   | 79 - >99**   |
| Gestational                             | Age (weeks)  |                    |                |   |  |
| ≥35 years<br>at EDD                     | 15 +   | 15 +               | 15 +           | 10 - 11 +   | 10 +   |
| Chromosom                               | al Abnormaliti   | es Detected        |                |   |  |
| All                                     | T21  | T21<br>T18         | T21<br>T18     | T21<br>T18  | T21, T18, T13<br>sex chromosome<br>aneuploidy***,<br>microdeletions*** |
|   | Coun. 2013;22(3):291-295<br>abibution , copyright reserved Quest | Diagnostics 2015   |                | * Nuchal translucency<br>** Applies to T21, T18, an<br>*** Some cases | Quest Diagnostics  |

### Current Options for Fetal Aneuploidy Screening

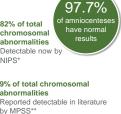




### Clinical Impact of NIPS

| Tota | al abnormal amniocentesis               | results =      | 2.3% | 0                                  |
|------|---|----------------|------|------------------------------------|
| An   | euploidy; Robertsonian transloca        | tion 1.86%     |      | 82% of t                           |
| •    | T21                                     | 1.16%          |      | chromos                            |
| •    | Sex chromosome aneuploidy               | 0.35%          |      | abnorma                            |
| •    | T18                                     | 0.23%          |      | Detectab                           |
|      | T13                                     | 0.07%          |      | NIPS*                              |
| •    | t(13:14)                                | 0.05%          | /    |                                    |
|      |   |                | _    | 9% of to<br>abnorma                |
|      | arker; unbalanced translocation<br>ther | 0.12%<br>0.09% | >    | Reported<br>by MPSS                |
| Ba   | alanced arrangements                    | 0.20%          | >    | 9% of to<br>abnorma<br>Unlikely of |

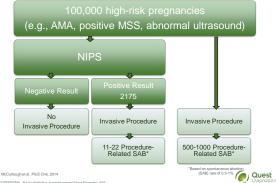
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### % of total chromosomal bnormalities

Inlikely detectable by MPSS\*\* NBPS: Nonhvashe prenatal screening MPSS: Massively parallel shotgun sequencing. MPSS: Massively parallel shotgun sequencing.

# Clinical Impact of NIPS



### Clinical Impact of NIPS on Invasive Prenatal Diagnosis

- Action from insight
   Provides invaluable insight for informed decisions with regard to electing CVS or amnicoentesis.
- Can be used as 1<sup>st</sup> tier screening (high-risk pregnancy) or 2<sup>nd</sup> tier screening (general and high-risk pregnancy)
- QNatal Advanced detection (sensitivity) rate = 100%
  - Validation series, confidence interval = 89.95% 100%
    General NIPS sensitivity rates range from 70% to 94%
  - Includes sex chromosome aneuploidy and microdeletions
- Higher positive predictive value (PPV) than MSS, NT, or a combination of both
- NIPS is screening; it is not diagnostic
  - False positives and negatives do occur; therefore, an invasive test is required to definitively confirm any positive result.

Benn PA. Obstet Gynecol. 2002;100(6):1168-1176 ; Malone FD. N Eng J Med. 2005;353:2001-2011 ;; Swanson A. Curr Genet Med Ret 2013;1(2):13-121 ;; Wang JC. Genet Med. 2014, doi: 10.1038/gim.2014.92.



### Clinical Complications of NIPS: False Positives and Negatives

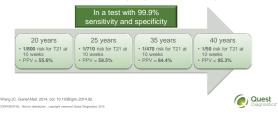
- · Confined placental mosaicism (CPM)
- · Co-twin demise/vanishing twin
- Fetal mosaicism
- Maternal mosaicism
- Maternal malignancy
- · Collection/laboratory error
- Directly related to prevalence (positive and negative predictive value)





### Positive and Negative Predictive Value (PPV and NPV)

- Unlike sensitivity and specificity, PPV and NPV are dependent upon condition prevalence
  - PPV: percentage of patients with a positive test who truly have the condition
     PPV (%) = (true positive) (true positive + false positive) x 100
- PPV for NIPS is lower in the general pregnancy population, as the incidence of chromosomal aneuploidy is lower in these patients:

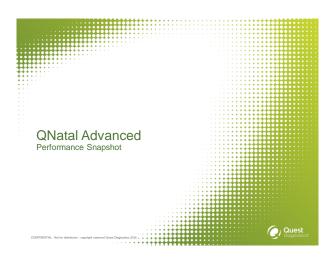


### Summary of ACOG, ISPD, and NSGC Recommendations

- NIPS should be included in prenatal testing options offered to high-risk patient population
- NIPS should be offered within the context of informed consent, education, and counseling by a qualified provider
- NIPS positive results should be followed by recommending an option for confirmatory diagnostic testing
   Negative results do not ensure an unaffected fetus

American College of Obstetriolans and Gynecologists Committee on Genetics. Obstet Gynecol. 2012;120:1532-1534 Devers PL. J. Genet Cour. 2013;22(3):291-296. Benn P. Prenat Diagn. 2012;32(1):1-2. OPERIONIR. Inter developed...committee memore Quart Discroting. 2015





# **QNatal Advanced Test Content**

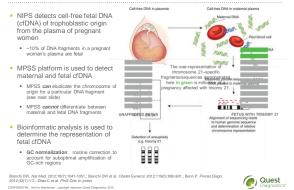
| Location        | Syndrome Name     | Estimated Frequency of Live Birth |  |
|-----------------|-------------------|-----------------------------------|--|
| Chromosome 21   | Down              | 1/800                             |  |
| Chromosome 18   | Edwards           | 1/6,000                           |  |
| Chromosome 13   | Patau             | 1/7,000-33,000                    |  |
| Chromosome X    | X, XXX, XXY, XYY  | 1/500                             |  |
| Sex Chromosomes | Sex Determination |                                   |  |
| 22q*            | DiGeorge          | 1/4,000                           |  |
| 1p*             | 1p36              | 1/10,000                          |  |
| 15q*            | Angelman          | 1/20,000                          |  |
| 15q*            | Prader-Willi      | 1/20,000                          |  |
| 5p*             | Cri-du-chat       | 1/50,000                          |  |
| 4p*             | Wolf-Hirschhorn   | 1/50,000                          |  |
| 11q*            | Jacobsen          | 1/100,000                         |  |
| 8q*             | Langer-Giedion    | Rare                              |  |

\*Microdeletion

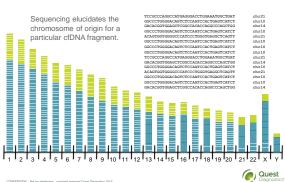
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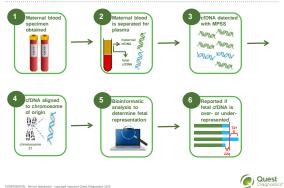
### Performance of QNatal Advanced



Performance of QNatal Advanced

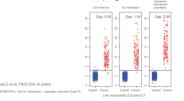


### Performance of QNatal Advanced



### Validation of QNatal Advanced: Z-score Calculation

- · Z-Score is used to determine positive/negative result for core trisomies E-Score is used to determine positive/negative result for one insome i.e., over-presentation of chromosome material vs. appropriate representation of chromosome material
   Z-Score: number of standard deviations from the mean (average)
   (standard deviation chromosome 21%)
   (standard deviation chromosome 21%)
- In assay development, all trisomies had Z-scores greater than 11 when fetal fraction was greater than 5%
- In validation, all unaffected pregnancies had Z-scores less than 4

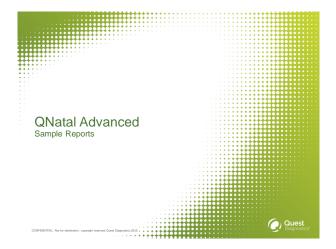




### Summary of QNatal Advanced

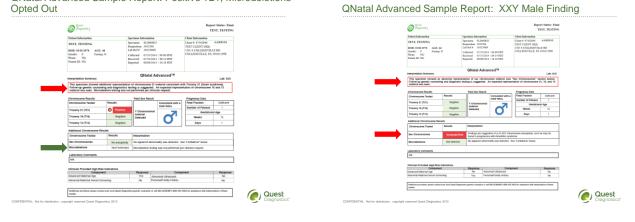
- Our laboratory-developed NIPS
- Can be performed as early as 10 weeks' gestation
   At any gestational age thereafter without restriction
- Whole genome massively parallel shotgun sequencing (MPSS)
- Measures and reports fetal fraction as either sufficient or insufficient for analysis using a 5% cut-off
- Binary positive/negative result for core trisomies (T21, T18, T13)
- Clear reporting of sex chromosome aneuploidy and microdeletions as additional, incidental findings
- Opt out selections for microdeletions and fetal sex
- · Validated for use in twin gestation
- 1-2% "no call" rate based on internal validation data





| QNatal Advanced Sample Report: | : Clear and Concise |
|--------------------------------|---------------------|
| Negative, Fetal Sex Opted Out  | Negative, Female    |
|                                |                     |

| C Bagnasting  |  |   |   |  | ST, TESTING         | Care Care  |                          |   |                         |  | oort Status: Fi<br>TEST, TESTE |
|---|--|---|---|--|---------------------|--|--------------------------|---|-------------------------|--|--------------------------------|
| Potent Information Specimen Information                                   |  |   | Client Information  |  | Patient Information |  | Sportinue Information    |   | Chod Information        |  |                                |
| HENT, HENTENG<br>DOB: (0.012)70 AGE: 44<br>Geoder: F Facing N<br>Home: NO |  | Spectmen: \$2,000833<br>Requirem: \$83,359<br>Lob Ref: \$25559N<br>Collecut: \$75112914 / 08:00 PDT<br>Record: \$25112914 / 08:04 PDT<br>Reported: \$8502814 / 08:04 PDT<br>Reported: \$8502814 / 08:05 PDT |   | Charge 975(2040) AARRISS<br>TEST CLERNT (HQ)<br>1111 IS COLLEGEVILLE, PA 19428-2598<br>COLLEGEVILLE, PA 19428-2598 |                     | TEST, TESTING<br>DOR: 0./011975 AGE: 44<br>Gendre F F Faring: N<br>Phone: NG |                          | Openanes:         \$1,0008337           Reprintes:         \$132396           Lab Barlet:         \$132396           Collessel:         \$132398           Reprintes:         \$132398           Collessel:         \$132398           Reported:         \$132398           Reported:         \$64962814 / 1018 PDT           Reported:         \$64962814 / 3218 PDT |                         | Cline & STREERO AARESS<br>TEST CLEENT (HQ)<br>1251 S COLLOGYTILE RD<br>COLLEGEVILLE, PA 19436-2998 |                                |
|   |  | QNatal A  | dvanced <sup>1M</sup>   |  |                     |  |                          | ONatal Adv  | ~                       |  |                                |
| reportation Summary   |  |   |   |  | Later Set           | Interpretation Summary   |                          | QNatal Adv.   | inced                   |  | Lab St                         |
| This spectrum showed exp  | ected representation   | n of shremesome 2   | 1, 18, and 13 material.   |  |                     | This specimen showed of  | repected representation  | es of ethromosome 21, 1   | 8, 12 material.         |  |                                |
|   |  |   |   |  |                     | Chromosome Results   |                          | Fetal Sex Repuit  |                         | Programcy Data   |                                |
| Transistere Results   | Banada .   | Fetal Sex Reput   |   | Pregnancy Data   | Output .            | Chromoscene Tested   | (TR36R3                  |   | Consistent with a       | Fetal Fraction   | Sufficient                     |
| Overalize Tested  | RECUTS   |   |   |  | SURGER              | Trisony 21 (721)   | Negative                 | T (bernersen)   | female febus.           | Number of Petuses  |                                |
|   | Negative   | Vegative Cyted Out  | Petal sex<br>testing not<br>performed per<br>clinician<br>request | Number of Feb.ses<br>Gestebore<br>Thesis   |                     |  |                          | T Chromosonal   | 0                       | Gestation  |                                |
|   | Negative   | - Cyner Cox   |   |  |                     | Triscery 18 (T10)  | Nejative                 | Owtexted  |                         | Weeks  | 15                             |
| TINOTY 13 (T12)   | Negative   |   |   | 0211   | 1                   | Trisony 13 (T12)   | Nepilive                 |   |                         | Days   | 1                              |
|   |  |   |   |  |                     | Additional Chromosome  | Requits                  |   |                         |  |                                |
| Additional Chromosome Res   |  |   |   |  |                     | Chromosome Tested  | Results                  | Interpretation.   |                         |  |                                |
|   | A Results Interpretation   |   |   |  |                     | Sex Chromosomes  | No anexploid             | No apparent abnormally was detected. See "Limbations" being.  |                         |  |                                |
| Bes Chromosomes   | No areapoidy the apparent obnormality was detected, see "Limitations" below. |   |   |  |                     | Wannahalations   | Not deterind             | f to accord allocated your detected. See "LiveLators" teles   |                         |  |                                |
| Nursdelwoons.   | Not detected   | No apparent abro  | mally was detected. 5   | ee "Limitations" below.  |                     |  |                          |   |                         |  |                                |
| Laboratory Commands   |  |   |   |  |                     | Laboratory Comments  |                          |   |                         |  |                                |
| 62  |  |   |   |  |                     | n's  |                          |   |                         |  |                                |
| Clinician Previded High-Risk  | Indications  |   |   |  |                     | Clinician Provided High-<br>Comp   |                          | Engorne   | Comp                    |  | Danner                         |
| Component<br>Advanced Maternal Ace  |  | Pesponse  |   |  | Response            | Advanced Maternal Age  |                          |   | normal Ultracound       |  | NO                             |
| Advanced Maternal Age<br>Stevenski Maternal Server Sciencisto             |  |   | Abnormal Ultrasound<br>Personal Family History                    |  | No                  | Absornal National Server Screening   |                          | No Pe   | Personal/Family History |  | No                             |
| Healthcare providenc please co<br>interpretation of these results.        | that your local Gave   | Chapmontics gurantic o  | canador or call 666-GDM   | EMPO (885-406-3463) for annial   | inci with           | Taalikuur pooliime pisaar o<br>mada.   | nini yor loor (peni Cing | nation gradic coanadar ar   | al INCOMPTO JULIO       | 2007) for annihilator with inte  | prolation of Eleme             |



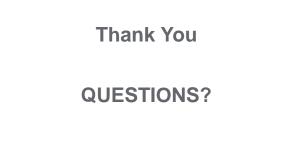
# QNatal Advanced Sample Report: Positive T21, Microdeletions Opted Out

| QNatal Advanced Sample | Report: Clear and Concise |
|------------------------|---------------------------|
| Negative, Male Twin(s) | Negative, Female Twins    |

| Diagnostic:                               |                                   |  |                         |  | et Status: Final<br>LST, TESTING | Const. Disputer  |                    |   |                         |  | Part Status: Fin<br>TEST, TESTIN |
|---|-----------------------------------|--|-------------------------|--|----------------------------------|--|--------------------|---|-------------------------|--|----------------------------------|
| Potient Information 2                     |                                   | per kanon India marikon  |                         | Climit Information   |                                  | Potent Information 5   |                    | Specimen Informatio   |                         | Climi Islamaton  |                                  |
| DOR-OVEDPTO AGE: 44                       |                                   | perianes: NLOBORNI<br>Inguistics: 3033364<br>ab Ref 8: 3023560<br>Milectel: 0731/2014 / 09:00 PDT<br>insuited: 0731/2014 / 09:00 PDT<br>inputed: 08/06/2014 / 10:14 PDT<br>inputed: 08/06/2014 / 10:14 PDT |                         | Clear F 9751286 AARESS<br>THEY CLEARY DRO<br>1501 S COLLEGEVILLE RD<br>COLLEGEVILLE, PA 19435-3992 |                                  | TENT, TENTING<br>ROB: 0.011 PPB AGE: 46<br>Gender: F Faring N<br>Plane: NG<br>Print ID: NG |                    | fpeciaeec 932060     force 9320     force 9320     force 9320     force 94     force 94 |                         | Chee # 1930280 AAR555<br>TRAT CLEDIT (HQ)<br>1211 5 COLLEGEVILLE RD<br>COLLEGEVILLE, PA 19405-2000 |                                  |
| Investation Receivery                     |                                   | QNatal Ar  | dvanced <sup>TM</sup>   |  | Lak B/C                          | Interpretation Reportery   |                    | QNatal Ad   | ranced <sup>TH</sup>    |  | Lat. B.C.                        |
| This specimen showed super                | ted representation                | of chromosome 2  | 1, 18, and 13 material. |  |                                  | This specimen showed expe  | and representation | of dysmosome 21   | , 18, and 13 material . |  | Cas and                          |
| Chromosome Results                        |                                   | Febri Sen Ren  |                         | Pressancy Data   |                                  | Chromosome Results   |                    | Factor Sales Press  | e                       | Pregnance Data   |                                  |
| Chromosome Tested                         | Assults                           | Yabramatar   | consistent              | Peter Praction   | Sufficient.                      | Chromosome Tested  | Results            |   | Considert with          | Petal Preston  | Sufficient                       |
| Trisonry \$1 (721)                        | madue                             | material dete  | cted with at least      | Number of Fetuses  | 2                                | Trisorry \$1 (721)   | Neutre             | T chromosom   | malityle female         | Number of Fetutes  | 2                                |
|   |                                   |  |                         | Oestational  | Age                              | 1.1.1  |                    | moderial not  |                         | Gestation  | al Age                           |
| Trisonry 18 (T18)                         | Negútivo                          | C C C  | 3-്ററ                   | Weeka  | 15                               | Trisonry 18 (T18)  | Negative           | detected  | <b>99</b>               | Viseia   | 15                               |
| Trisony 13 (T10)                          | Negative                          |  | •••                     | Otyn   | 1 Tracery (2 (710) Negative      |  |                    | + +   | Days                    |  |                                  |
| Additional Chromosome Res                 | é16                               |  |                         |  |                                  | Additional Chromosome Rep  | da la              |   |                         |  |                                  |
| Chromosome Tested                         | Results                           | Interpretation   |                         |  |                                  | Chromosome Tested  | Results            | Interpretation  |                         |  |                                  |
| Sex Chromosomes                           | No aneuptority                    | No apparent at   | normality and declected | See "Limbalcen" below.   |                                  | Sex Chromosomes  | No aneightedy      | No apparent abnormality was detected. See "Limitations" below   |                         |  |                                  |
| Microdeletions                            | Not detected                      | No apparent abnormality was dedicated. Gee "Limitations" below.  |                         |  |                                  | Manderstons  | Not dehedred       | No apparent atmormality was detected. See "Limitations" below.  |                         |  |                                  |
| Laboratory Comments                       |                                   |  |                         |  |                                  | Laboratory Comments  |                    |   |                         |  |                                  |
| nia                                       |                                   |  |                         |  |                                  | nia  |                    |   |                         |  |                                  |
|   |                                   |  |                         |  |                                  |  |                    |   |                         |  |                                  |
| Clinician Provided High-Risk<br>Companies | rdications                        | finance.   | Carro                   |  | Response                         | Clinician Provided High-Risk<br>Company  | Indectors          | Paspinsa  |                         | and a local second   | Response                         |
|   |                                   | Yes  | Abrormal Ultracound     |  | No                               | Advanced Material App  |                    |   | Absorbal Unisound       | 0.947  | No                               |
| Advanced Material Apr                     | Abnormal Nuternal Serum Screening |  | No Propart and viscov   |  | N                                | Almonthal Malernal Scium Screening   |                    |   |                         | dFamily Hidary   |                                  |

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