Informed Consent for Invitae Chromosomal Microarray Analysis, Karyotype Analysis and FISH Analysis

FM188-1

1. CHROMOSOMAL MICROARRAY ANALYSIS:

- Chromosomal microarray analysis (CMA) is a genetic test that may be recommended by my healthcare provider for a number of different reasons:
  i. Testing of a baby, child or adult with learning difficulties, intellectual disabilities, autism spectrum disorder, or multiple birth defects
  ii. Testing of an ongoing pregnancy
  iii. Testing of tissue from a miscarriage or stillbirth
  iv. Testing of an individual with infertility or sub-fertility
  v. Testing of an individual who has a blood relative with a chromosomal copy number variant
- Sometimes, a karyotype or FISH analysis is ordered in conjunction with or instead of CMA. Information about karyotype or FISH analysis follows the description of CMA.

1A. CMA DESCRIPTION AND LIMITATIONS:

- CMA is designed to identify losses or gains of chromosomal information called copy number variants (CNVs) that can cause problems in physical and/or intellectual development.
- CMA can also identify areas of chromosomes in which there is less variation than expected. These are called regions of homozygosity (ROHs) and may be observed when both parents pass on genetically identical chromosomal regions or these regions are inherited from a single parent. ROHs do not involve a loss or gain of chromosomal information, but may indicate other issues to consider, such as shared ancestry or imprinting disorders.
- Invitae's CMA uses single nucleotide polymorphisms (SNPs) to evaluate all 23 pairs of chromosomes for CNVs and ROHs.
- Limitations of CMA include the inability to detect balanced chromosomal rearrangements (in which no chromosomal information is lost or gained), CNVs that are smaller than the stated resolution of the test, and low level mosaicism (meaning that there is a mixture of cells with different chromosomal composition).

1B. CMA RESULTS AND INTERPRETATION:

- An **Abnormal/Positive result** indicates the identification of one or more clinically significant CNVs associated with a known chromosomal or genetic disorder, or the presence of one or more ROHs, which may represent shared ancestry or a possibile imprinting disorder.
- A **Normal/Negative result** indicates that no clinically significant CNVs or ROHs were identified. It is important to note that:
  i. An individual can have a normal microarray result and still have a genetic syndrome or chromosomal disorder.
  ii. Some regions of the genome show variability in the amount of chromosomal information present, but these CNVs have not been associated with any recognized developmental or health effects. This type of normal human genetic variation is referred to as a *benign* CNV. Because benign CNVs are not associated with any chromosomal disorders, they are not included on CMA reports.
- A **Variant of Uncertain Significance (VUS)** result typically indicates that a CNV has been identified that is not known to be benign but has also not been associated with any specific disorders. A VUS result may also represent a CNV that is considered to be a risk factor for developmental disorders and/or birth defects but has also been identified in healthy individuals. A VUS result may lead to a recommendation for additional testing or the genetic testing of additional family members.
  i. If parental studies are performed and the individual tested is not a blood relative of the patient (i.e., misattributed paternity), this can lead to an inaccurate interpretation of the patient's results.
- No testing apart from that which is ordered will be performed. Additional testing requires my additional, express consent.

2. KARYOTYPE ANALYSIS:

- Karyotype analysis is a chromosomal test that may be ordered by my healthcare provider in conjunction with, or instead of CMA. Common reasons for ordering a karyotype include:
  i. Testing of an ongoing pregnancy
  ii. Testing of an individual with infertility or sub-fertility
  iii. Testing of an individual with a family history of a chromosomal abnormality
  iv. Testing of a baby, child or adult with learning difficulties, intellectual disabilities, autism spectrum disorder, or multiple birth defects

2A. KARYOTYPE DESCRIPTION AND LIMITATIONS:

- Karyotyping is designed to identify changes to the number and structure of the chromosomes. Having more than or fewer than 46 chromosomes is called *aneuploidy*. Structural changes involve the loss, gain or movement of a chromosomal segment to another chromosome (i.e., a translocation).
- Unlike CMA, karyotyping can identify balanced chromosomal rearrangements; meaning swapping of segments of chromosomes without the loss or gain of any information.
- Limitations of karyotyping include the inability to routinely identify CNVs smaller than 5-10 Mb, ROHs, and low level mosaicism.

2B. KARYOTYPE RESULTS AND INTERPRETATION:

- An **Abnormal/Positive result** indicates that an alteration to the number or structure of one or more chromosomes has been identified. Unbalanced rearrangements typically result in an abnormal phenotype in the patient, however, balanced rearrangements may only be associated with recurrent miscarriages or fertility issues. If it is not clear whether the alteration is balanced or unbalanced, follow-up testing may be required, which may include parental studies, molecular testing, or fluorescence in situ hybridization (FISH) studies.
- A **Normal/Negative result** indicates that no numeric or large structural changes were identified (within the limits of detection of the test). It is important to note that:
  i. An individual can have a normal karyotype result and still have a genetic syndrome or chromosomal disorder.
  ii. Some regions on our chromosomes show variations of size or chromosomal orientation that are known to be present in the general population and have not been associated with any recognized developmental or health effects. Such variations are considered benign.
- No testing apart from that which is ordered will be performed. Additional testing requires my additional, express consent.

3. FLUORESCENT IN SITU HYBRIDIZATION (FISH):

- FISH analysis may be ordered by your healthcare provider in conjunction with other chromosomal studies.
  i. Testing of an ongoing pregnancy
  ii. Testing of an individual with infertility or sub-fertility
  iii. Testing of an individual with a family history of a chromosomal abnormality
  iv. Testing of a baby, child or adult with learning difficulties, intellectual disabilities, autism spectrum disorder, or multiple birth defects

3A. FISH ANALYSIS DESCRIPTION AND LIMITATIONS:

- Interphase FISH is designed to count the number of chromosomes 13, 18, 21, X and Y, which represent common prenatal aneuploidies.
- Limitations of interphase FISH are that it does not evaluate these chromosomes' structure and does not evaluate any other chromosomes.
- Metaphase FISH is used to evaluate specific structural chromosomal rearrangements; typically following an abnormal CMA or karyotype in the patient or a family member.
- Unlike chromosomal microarray analysis (CMA), metaphase FISH can identify balanced chromosomal rearrangements; meaning exchange of segments of chromosomes without the loss or gain of any chromosomal information.
- Metaphase FISH's primary limitation is that it is focused only on the region being evaluated and does not evaluate abnormalities outside of these specific regions.

3B. FISH ANALYSIS RESULTS AND INTERPRETATION:

- An **Abnormal/Positive result** indicates that an alteration to the number or structure of one or more chromosomes has been identified. With interphase FISH, this would indicate an aneuploidy of one of the five chromosomes evaluated. With metaphase FISH this may indicate additional structural rearrangement of chromosomal information.
- A **Normal/Negative result** indicates that no abnormalities were identified. For interphase FISH, this would mean a normal number of chromosomes 13, 18, 21, X and Y. For metaphase FISH this would mean that the specific change that is being evaluated is not present.
- Rarely, a **result of Uncertain Significance** may occur when the presence or absence of a structural chromosomal abnormality is unclear based on the FISH results.

4. **INCIDENTAL FINDINGS:** In the course of processing the ordered tests, Invitae may find changes in genes that are unrelated to the clinical concern that prompted my having the test but are clearly associated with a significant risk for disease and could therefore negatively impact my own health and/or the health of my close relatives. These are known as "incidental findings." Invitae will report such incidental findings when (and only when) there are accepted medical interventions available that can prevent or treat the health consequences of these genetic changes.

5. **DISCLOSURE OF TEST RESULTS:** Invitae's clinical reports are released only to the certified healthcare professional(s) listed on the test requisition form. Clinical reports are confidential and will only be released to other medical professionals with my explicit written consent. It has been explained to me that my clinical report is available for me upon request after it has been released to my healthcare provider or upon request in accordance with applicable law.

6. **RISKS AND LIMITATIONS:** My healthcare provider has explained the effectiveness and limitations of the test(s), and I understand that the test results may not provide definitive conclusions regarding risk. While this testing is highly accurate, rare testing errors may occur. Further testing may be warranted for myself or my partner and this additional testing may or may not be covered by insurance. Sometimes for technical reasons, results cannot be generated. Additional samples may be needed if results are not generated.

7. **PRIVACY:** I understand that my data and personal information will be stored and protected in compliance with applicable regulatory requirements (e.g., HIPAA and equivalent protections), and I acknowledge that I have read and understand Invitae's Privacy Policy and Notice of Privacy Practices (available at www.invitae.com/privacy).

8. **NONDISCRIMINATION:** There are state and federal laws that prohibit discrimination against individuals for the purpose of employment or obtaining health insurance and that prohibit insurers and employers from seeking an individual's genetic information without consent. In accordance with such laws, Invitae will not disclose or interpret my genetic information for use by employers or insurers. However, it is my responsibility to consider the possible impact of my test results as they relate to insurance rates, obtaining disability or life insurance, and employment. The Genetic Information Nondiscrimination Act (GINA), a US Federal law, provides some protections against genetic discrimination. For more information on GINA, visit www.genome.gov/10002328.
9. **GENETIC COUNSELING:** I understand that Invitae recommends that I consult with a genetic counselor before consenting to this test and a genetic counselor or my healthcare provider about my results. For a list of medical geneticists and counselors who may be available in my area, I may visit the National Society of Genetic Counselors website at www.nsgc.org. Further testing or additional physician consults may be warranted.
10. **RESEARCH:** Sharing de-identified genetic data can significantly accelerate medical research for both individual patients and society as a whole. Invitae encourages patients to choose to share their genetic variants with the medical and scientific community to help accelerate our understanding of genetic conditions, improve genetic testing, find new therapies, and eventually prevent disease. Invitae will share results after they are de-identified, meaning that Invitae removes any information that identifies or could be used to identify me personally.
    a. **De-identified genetic information:** I understand Invitae may store and retain indefinitely at its discretion, except as prohibited by law, and use and/or disclose to third parties, including public databases, my de-identified genetic information for quality assurance, test development and/or validation, research, and/or educational purposes.
    b. **De-identified samples:** I understand Invitae may store and retain indefinitely at its discretion, except as prohibited by law, and use and/or share with third parties my de-identified samples for quality assurance, test development and/or validation, research, and/or educational purposes.
    c. **Future contact regarding research:** I permit Invitae to contact me in the future about research opportunities that may be related to my condition or my test results.

    All patients (other than residents of those states specifically identified below): I control how Invitae uses my data. I understand that I can contact Invitae at privacy@invitae.com if I would like to change my preferences with respect to how Invitae uses my deidentified data. If I choose to restrict the use of my de-identified genetic information or sample(s): (a) I understand that to the extent that such information has already been used or shared, it cannot be retracted or destroyed, and (b) I understand that my de-identified genetic information and/or sample(s) may still be used for quality assurance, test development and/or validation; shared with public databases; and/or (in connection with de-identified information) used or disclosed to third parties, not on an individual basis but as aggregated information for research or education purposes.

    Residents of New York or Alaska: I understand that my sample(s) (or my minor child's sample(s)) shall be destroyed no more than 60 days after they were taken or at the end of the testing process, whichever occurs later, unless a longer period of retention is expressly authorized. I understand that I can authorize a longer period of sample retention by contacting Invitae at privacy@invitae.com. I understand that if I authorize my samples to be retained longer, I can also allow the use of my de-identified samples for research and/or education by contacting Invitae at privacy@invitae.com. If I do not opt in, I understand that my de-identified samples will not be used for quality assurance, test development and/or validation; nor and/or used, disclosed to, or shared with third parties for research or education purposes. I further understand that I can allow the use of my de-identified genetic information for research and/or education, or to allow Invitae to contact me in the future regarding research opportunities by contacting Invitae at privacy@invitae.com. If I do not opt in, I understand that my de-identified genetic information may still be used for quality assurance, test development and/or validation; shared with public databases; and/or used, disclosed to, or shared with third parties, not on an individual basis but as aggregated information, for research or education purposes.

    Residents of Florida, Massachusetts, Minnesota, New Hampshire, Texas, Vermont and countries other than the United States: I understand that I can contact Invitae at privacy@invitae.com to opt-in to allow the use of my de-identified genetic information or samples for research and/or education, or to allow Invitae to contact me in the future regarding research opportunities. If I do not opt in, I understand that my de-identified genetic information and/or samples may still be used for quality assurance, test development and/or validation; shared with public databases; and/or used, disclosed to, or shared with third parties, not on an individual basis but as aggregated information, for research or education purposes.
11. **RECONTACT FOR CLINICAL UPDATES:** I understand that knowledge of genetic information will improve over time, that new information may become available in the future that could impact the interpretation of my results, and that Invitae may notify me of clinical updates related to my genetic profile (in consultation with my primary clinician as indicated). I may request additional notifications and resources relevant to my genetic profile by contacting Invitae at privacy@invitae.com.
12. **NON-COVERED SERVICE:** In the event my insurer denies coverage for this test for any reason, including deeming the test to be a non-covered service or not medically necessary, I agree that Invitae may bill me directly for this service and I will remit payment directly to Invitae.

13. **TESTING IS VOLUNTARY:** I understand that my consent to testing is voluntary, and I may choose not to have my sample tested.
14. **COPY OF THIS FORM:** I have a right to receive a copy of this form.

BY SIGNING BELOW, I ATTEST TO THE FOLLOWING:

1. I have read (or had read to me), and that I understand, the information provided in this consent;
2. I have all the information I want, and all my questions have been satisfactorily answered; and
3. I hereby consent to microarray analysis and/or karyotype analysis as ordered by my healthcare provider.

Patient signature	Date
Patient name (please print)	Email address

HEALTHCARE PROVIDER STATEMENT

By signing below, I attest that:

1. I am the referring physician or authorized healthcare provider;
2. I have explained the purpose of test described above;
3. The patient has had the opportunity to ask questions regarding this test and/or seek genetic counseling; and
4. The patient has voluntarily decided to have this test performed by Invitae.

Healthcare provider signature	Date