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»Frequently Asked Questions for Physicians

What is array CGH?

Array-based comparative genomic hybridization (array CGH), also called microarray analysis, is a new cytogenetic technology that evaluates areas of the human genome for gains or losses of chromosome segments at a higher resolution than traditional karyotyping. Whereas traditional high-resolution chromosome analysis detects chromosome structure alteration at a resolution of 5 megabases (Mb) or greater, array CGH detects gains or losses of DNA, also called *DNA dosage alterations*, that cannot be seen by traditional karyotyping and may sometimes be only thousands of basepairs in size.

How does it work?

Segments of DNA are selected from public genome databases based upon their location in the genome. The clones are predominantly selected to target areas of the human genome that, when deleted or duplicated, are known or highly suspected to cause well-characterized genetic conditions with mental retardation and/or birth defects. Microarray printers attach the clones to a glass slide in an organized fashion to form a microarray. A typical microarray slide contains thousands of different clones representing targeted areas of the genome. Fluorescently labeled DNA from both patient and a known normal human control are applied to the slide and compete to attach or *hybridize* to their corresponding BAC clone DNA segments. Computer software analyzes the fluorescent signals for areas of unequal hybridization of patient versus control DNA, signifying a DNA dosage alteration (deletion or duplication).

Are there different types of probes used for array CGH?

The two probes most commonly used for array CGH for the detection of constitutional chromosomal abnormalities are bacterial artificial chromosome (BAC) clones and oligonucleotide probes. Both types of probes have advantages and disadvantages. BAC's, which are usually 80-200 kb, may miss alterations smaller than the size of a clone but are less likely to detect alterations of unclear clinical significance. Oligonucleotides, which are much smaller probes, usually 25-60 bp, may detect small alterations that would not be seen using a BAC microarray, but oligonucleotide arrays are more likely to detect small alterations of unclear clinical significance.

Why is FISH visualization of probes important?

FISH confirmation of abnormalities detected by a microarray requires that the probes be validated to ensure they map to the correct location in the genome prior to their use on the microarray, or for oligonucleotide arrays, that FISH validated probes corresponding to each region represented on the array are available. FISH visualization is essential for accurate diagnosis and recurrence risk estimation. It provides information about the nature and causative mechanism of the chromosome alteration.

What types of abnormalities does array CGH detect?

Array CGH detects microscopic and submicroscopic deletions and duplications at targeted areas of the genome, including loci of known microdeletion/microduplication syndromes, subtelomeric regions, and pericentromeric regions. Array CGH will also identify marker chromosomes, some cases of mosaicism, and aneuploidy.

What will array CGH not detect?

Array CGH will not detect balanced chromosome rearrangements, such as balanced translocations or inversions. Array CGH will not detect alterations in chromosome structure at areas of the genome not covered by the array. This technology will not detect sequence alterations or single-basepair mutations. Array CGH will not detect mosaicism at a level lower than 20%, nor will it detect some types of polyploidy, such as triploidy.

I already order subtelomere probes on many of my patients. Why perform microarray testing instead of FISH with subtelomere probes?

Array CGH offers more comprehensive analysis of the subtelomeric regions and can identify terminal *and* interstitial deletions, whereas subtelomeric probes only identify terminal deletions. Furthermore, array CGH can help to determine the size of the subtelomere deletion or duplication. The SignatureChip® has on average > 5 Mb of coverage on each subtelomere. In our experience, an estimated 25% of subtelomeric alterations identified through our laboratory have been interstitial and would be missed by conventional subtelomeric probe analysis.

I have a patient with MCA and an apparently balanced de novo translocation. Can the SignatureChip™ help determine whether it is really balanced?

Array CGH will not detect balanced rearrangements. This technology may detect submicroscopic deletions or duplications at a breakpoint if the breakpoint occurs in an area covered by the microarray. Please call our laboratory to discuss this type of case before sending a sample.

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Who is a candidate for array CGH?

Patients with or without prior genetic workup who have mental retardation of unknown etiology, autism, congenital anomalies, dysmorphic features, a suspected syndrome with normal chromosomes/subtelomere FISH/other studies, stillbirth or fetal demise.

What about testing a pregnancy?

Prenatal cases in which karyotype or FISH analysis is warranted can benefit from the newly designed Signature PrenatalChip® in addition to traditional chromosome analysis. The Signature PrenatalChip® is specifically designed to enhance prenatal cytogenetic testing while minimizing the possibility of results of unclear clinical significance. In some cases it may be beneficial to test using the SignatureChipWG™ or SignatureChipOS™. Please call our laboratory to discuss the appropriate microarray for your patients.

How do you handle cases of unclear clinical significance?

Our microarrays are designed to minimize polymorphic alterations. In the event that a result of unclear clinical significance is found, the patient report will identify the finding as having unclear clinical relevance. Signature Genomic Laboratories also participates in internal and external collaborations to define these regions and frequently publishes its findings in scientific journals.

What are the detection rates for your clinical loci?

Detection rates vary from locus to locus. They are based on current peer-reviewed literature and are available at our website with educational links at www.signaturegenomics.com. Board-certified genetic counselors are also available to discuss detection rates with you. For many loci tested by the SignatureChip® or Signature PrenatalChip®, a negative result does not exclude the suspected clinical diagnosis.

What types of samples are suitable for array CGH?

Array CGH is most commonly performed on whole blood samples. We require both a green-top sodium heparin tube and a purple-top EDTA tube. Array CGH can also be performed on cultured lymphocytes, cultured fibroblasts, placental tissue/POC, cultured amniotic fluid cells, cultured CVS samples, extracted DNA, and other samples. Please call the laboratory for more details.

Why do you need to know the gender of the patient?

Knowing the gender of the patient allows us to use the proper controls for quality assurance purposes.

Does insurance cover testing?

Many insurance providers cover array CGH, and CPT codes have been established specifically for microarrays. We will bill private insurance companies and all State Medicaid Programs. Other methods of payment, including institutional billing and self-pay, are also available. Visit our web site for more details regarding payment options.

How can I get more information?

Visit our website at www.signaturegenomics.com, e-mail us at info@signaturegenomics.com, or call us at 1-877-SigChip (744-2447).

In accordance with Washington State Law RCW 7.70.050 and WAC 388-531-0050, providing patients with the information necessary for them to be able to give their informed consent for testing or treatment is the responsibility of the health care provider who has direct contact with the patient. Laboratory tests are ordered and prescribed by physicians so it is the physician, not the laboratory, that is required to obtain the patient's informed consent for testing.