anora™
miscarriage test (POC)

Frequently Asked Questions

What does Anora do?

More than 50% of miscarriages are caused by a chromosome abnormality. Anora™ looks at fetal tissue (also called 'products of conception' or 'POC') after a miscarriage to find out if a chromosome abnormality was the likely cause of the loss. Natera offers Anora fresh and paraffin kits to allow for testing on current and prior losses.

Why use Anora?

For patients, Anora can help explain the reason for the loss, alleviate self-blame, and help with the healing process. It can also influence a patient's future reproductive decisions by providing information about recurrence risk and/or parental origin of chromosome abnormalities. For physicians, it can help provide much needed answers to their patients and reduce or define the patient care path.

What can Anora (fresh tissue) testing detect?

- Whole chromosome aneuploidy (a missing or an extra chromosome)
- Triploidy (an extra full set of chromosomes)
- Tetraploidy (detectable in the 3:1 form)
- UPD (uniparental disomy) of a single chromosome pair (two copies of a chromosome from one parent and no copies from the other; isodisomy or heterodisomy of the UPD can be determined)
- Full/complete paternal UPD (two sets of chromosomes originating from the father with no maternal DNA contribution. Isodisomy or heterodisomy can be determined)
- Full or partial maternal cell contamination (MCC) (ability to differentiate maternal vs. fetal results; requires a parental sample to be submitted)
- Deletions and duplications greater than 5 Mb
- Any terminal deletion or duplication is reported as this could be an indication for a balanced translocation in a parent
- Any deletion that is 1 Mb or greater and any duplication that is 2 Mb or greater is reviewed by a genetic counselor/geneticist and reported if clinically significant for cause of a miscarriage or reproductive recurrence risk

Microdeletions/microduplications that are always reported if found:

- 1p36 deletion
- 1q21.1 deletion (epilepsy)
- 2q37 deletion
- 3q29 terminal deletion
- 4p16.3 deletion (Wolf-Hirschhorn syndrome)
- 5p15.2 deletion (Cri du Chat)
- 7q11.23 deletion (Williams syndrome)
- 8q23.2-8q24.1 deletion (Langer-Giedon)
- 9q34 deletion
- 11p13-14 deletion (WAGR)
- 11q24.1 deletion (Jacobsen syndrome)
- 10p13-p14 deletion (DiGeorge 2)
- 15q11-q13 deletion (Prader-Willi/Angelman region)
- 16p11.2 deletion (epilepsy)
- 17p11.2 deletion (Smith-Magenis)
- 17p13.3 deletion (Miller-Dieker)
- 17q21.31 deletion
- 22q13 deletion (Phelan-McDermid syndrome)
- 22q11.2 deletion (DiGeorge/VCFS)
- 22q11.2 duplication
- Xq28 deletion (MECP2 deletion)
- Xq28 duplication (MECP2 duplication)

How does Anora work?

Anora runs POC tissue on a single nucleotide polymorphism (SNP) microarray looking for aneuploidy, deletions/duplications, and UPD (uniparental disomy) in the tissue sample. With a parental sample, Anora can determine the parental origin of an abnormality and rule out MCC. Analysis and interpretation are performed using Natera's proprietary algorithm.

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What are Anora's limitations on fresh tissue?

Anora cannot detect balanced chromosome rearrangements (inversions or balanced translocations). Balanced rearrangements typically do not cause miscarriage, but can be incidental findings on traditional karyotypes. These rearrangements have the normal amount of chromosomal material though it may be arranged differently. These changes likely cause no health problems for the individual carrying the rearrangement, but could predispose their offspring to a chromosomal abnormality.

What are Anora's limitations on paraffin embedded tissue?

Anora's paraffin test has three additional limitations. Triploidy of maternal origin cannot be distinguished from maternal cell contamination, so this form of triploidy may be missed. Deletions and duplications of chromosome segments are also not detectable. In addition, a higher percentage of paraffin tests will be either MCC or incomplete results. Incomplete results can mean there is not enough fetal DNA on the block/slides provided and so a result cannot be given. Paraffin testing requires both a maternal and paternal blood/buccal sample.

What type of sample should be collected for Anora fresh kits?

To run a successful Anora test, acceptable tissue includes chorionic villi, gestational sac, fetal skin/tissue, umbilical cord tissue, cord blood, and cytogenetic tissue cell pellets.

Why do we ask for a parent's sample along with the tissue sample?

Having a parental sample allows us to rule out MCC and determine parental origin of an abnormality. Natera can still run the fetal sample without a parent's sample and results will not be delayed; however, a 46,XX result cannot be ruled out as originating from maternal tissue. This would not allow for a conclusive result for fetal chromosomes. In addition, if an abnormality is identified, parent of origin cannot be determined which may offer additional information when parental chromosomes are a recommended follow-up test. Therefore, it is best to get the parental sample when the fetal sample is collected.

Is blood or buccal better for a parent's sample?

Blood from the mother or father is preferred. A buccal swab can be used if blood cannot be drawn. However, there is a risk for the sample to be unable to be analyzed, which would require another sample.

What is the appropriate parental sample for each Anora kit and patient situation?

See below for the recommended parental samples.

Patient Situation	Anora Kit (Fresh or Paraffin)	Sample Type
Miscarriage – fresh tissue collected (no egg donor/ sperm donor/surrogate used)	Anora Fresh	• **Preferred**: Paternal or maternal blood • **If unavailable**: Paternal or maternal buccal swab
Miscarriage – fresh tissue collected (egg donor/ surrogate used)	Anora Fresh	• **Preferred**: Paternal or egg donor (biological) blood • **If unavailable**: Paternal or donor buccal swab • **If unavailable**: Gestational carrier blood or buccal can be sent to rule out MCC (but would not be able to determine origin of abnormality)
Miscarriage – fresh tissue collected (sperm donor used)	Anora Fresh	• **Preferred**: Maternal or sperm donor (biological) blood • **If unavailable**: Maternal or donor buccal swab
Previous miscarriage – slides or block available	Anora Paraffin	• **Required**: Paternal and maternal blood • **If unavailable**: Maternal and paternal buccal swab will be accepted

What type of sample should be collected for paraffin testing?

For paraffin kits, both maternal and paternal blood samples are required. The paraffin sample can be accepted as either 10 serial slides: 1 H&E stained slide as a tissue source reference and 9 unstained slides (result turnaround time is about 2 to 4 weeks); OR as a formalin-fixed sample in a paraffin block (result turnaround time is about 4 to 6 weeks). If available, a pathology report is requested.

Where should Anora kits be stored?

Anora kits can be stored at a physician's office, at a surgery center, or at a hospital. The best location for Anora kits is wherever D&C (dilation and curettage) procedures take place.

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Do kits have expiration dates?

Yes. The expiration dates for the EDTA tube and the fresh tissue collection cup are listed on the left side of the box on the fresh kit. The nomenclature for the EDTA tube is “E,MMDDYY,” and the nomenclature for the collection cup is “F,MMDDYY.” The expiration for a paraffin kit is listed on the right side of the box and is titled “Expiration Date.”

How should the sample be stored?

Tissue and patient samples should be shipped to Natera as soon as possible. Tissue samples should be stored in the refrigerator overnight until the next possible shipping day. The blood tube (EDTA purple top tube) can be stored in the refrigerator for up to seven days. The buccal swab can be stored in the refrigerator for up to 72 hours.

For cord blood or tissue samples, do these need to go in a special container or do both go in the standard collection kit?

Cord blood needs to go in an EDTA purple top tube. Cord tissue or fetal skin can be placed in the saline POC cup like any other tissue.

Can a patient collect tissue at home?

Yes. If a patient has a miscarriage at home, the tissue can be collected and brought in to their doctor’s office to have it sent to Natera. The at home collection instructions can be found on the Natera website (www.natera.com).

How long is a fresh POC sample viable after collection?

While there is no set timeframe, tissue becomes less viable the longer it has been out of the body. Generally, Natera does not accept tissue samples that were collected more than 14 days ago. This guideline assumes the sample was stored in saline and kept refrigerated at 4 degrees C. If the sample was improperly stored (such as frozen, exposed to high temperatures, or stored in formalin), Natera would not be able to accept the sample.

However, if the tissue was placed in formalin, the pathology lab should be able to parrafinize the sample. Natera could then perform an Anora paraffin test on the sample with submission of both biological parental samples.

What is the minimum gestational age for Anora?

A gestational age of 6 weeks or greater is best; however, Natera has achieved results at 5 weeks gestation. Sending earlier losses is at the discretion of the doctor. The earlier the loss, the higher the chance for MCC.

What is the turnaround time for Anora?

The turnaround time for Anora fresh kits is about 1 week. The turnaround time for Anora paraffin kits is longer; 2-4 weeks for slides and 4-6 weeks for a paraffin block.

Why is Natera’s SNP microarray better than other testing methods available?

Karyotyping requires cells to be cultured which often results in long turn-around time (2-5 weeks). There is also a 10-40% risk of no results due to culture failure, and karyotyping cannot rule out MCC. Array CGH and other SNP arrays do not automatically detect complete MCC; this has to be ordered separately. Array CGH also does not detect some forms of polyploidy.

Why does MCC happen?

MCC occurs for several reasons. Fetal tissue represents <1% of tissue in a first trimester loss. In addition, maternal and fetal tissues can look similar, so it may be difficult to isolate adequate fetal tissue. A D&C after a loss may result in more fetal tissue obtained vs. someone miscarrying at home. Sorting for fetal tissue at the center before submitting the sample may also help reduce MCC results. The gestational age of the pregnancy and how long ago the fetal demise happened prior to sample collection can also affect the amount and quality of the tissue available.

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What are the limitations of Anora when a parental sample is not submitted?

Cannot definitively rule out MCC. When a lab does not collect a parental sample, cases of complete MCC may be falsely concluded to have normal female fetal results. Cases with partial MCC (mixture of maternal and fetal DNA in the tissue tested) may be missed or misdiagnosed as mosaic.

Cannot confirm complete molar pregnancy. A complete molar pregnancy is when an egg with no genetic information is fertilized by a sperm that duplicates (isodisomic) or is fertilized by two sperm (heterodisomic). This results in 46 chromosomes (the right number of chromosomes) BUT all are paternal in origin, which is called complete paternal UPD. Isodisomic forms may be difficult to confirm and heterodisomic forms would be missed entirely without a parental sample. Rare cases of complete molar pregnancies are chromosomally normal with another genetic mechanism. Identification of miscarriages caused by complete paternal UPD is important for maternal medical management.

Cannot determine parental origin of triploidy. Triploidy is an entire extra set of chromosomes (69 chromosomes total). The extra set of chromosomes can be maternal or paternal in origin. The parental origin is important for identifying partial molar pregnancies which are only associated with triploidy of paternal origin. Identification of pregnancies with paternal triploidy is important for medical management.

Cannot detect heterodisomic UPD of individual chromosome pairs. Heterodisomic UPD is when the two copies of a chromosome pair are not identical, but have the same parent of origin (e.g., both copies of chromosome 15 are maternal in origin). This can happen in a trisomy rescue event where an embryo/fetus has a trisomy and then one of the three chromosomes drops out (e.g., an embryo begins with trisomy 15 composed of two maternal copies of chromosome 15 and one paternal copy of chromosome 15 with subsequent dropping out of the paternal chromosome 15). The cause of a loss may be due to the UPD alone if select chromosomes are involved or may be an indication for a cause if a subset of cells retained the third copy of the chromosome and are trisomic.

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part of the Natera
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panorama™ prenatal screen | horizon™ carrier screen | spectrum™ preimplantation genetics (PGS/PGD) | anora™ miscarriage test (POC)

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