Clinical Features:
Fanconi anemia (FA) is a chromosomal instability disorder associated with congenital anomalies, progressive bone marrow failure, and cancer predisposition [1]. The most commonly described anomalies include thumb and radial bone abnormalities, short stature, and skin hyperpigmentation [1]. Some patients lack these characteristic physical features and present with bone marrow failure or cancer [2]. Associated cancers include acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and solid tumors of the head, neck, skin, gastrointestinal tract, and genital tract [1]. The majority of cases of FA are inherited in an autosomal recessive manner, with the exception of FANCB (X-linked) and RAD51/FANCR (autosomal dominant).

Our Fanconi Anemia Sequencing Panel includes sequence analysis of all 18 genes listed below. Our Fanconi Anemia Deletion/Duplication Panel includes deletion/duplication analysis of all 17 genes listed in bold below.

### Fanconi Anemia Sequencing Panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1(FANCS)</td>
<td>Recently, two cases of individuals harboring biallelic deleterious BRCA1 mutations were reported [3, 4]. Detailed phenotypic and cellular characterization of one patient provided lines of evidence supporting the hypothesis that biallelic BRCA1 mutations cause a new Fanconi anemia subtype associated with increased breast and ovarian cancer susceptibility [3].</td>
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<tr>
<td>BRCA2 (FANCD1)</td>
<td>Homozygous or compound heterozygous mutations in BRCA2 are associated with FA complementation group D1. BRCA2 mutations are associated with early-onset leukemia and solid tumors, and a high rate of spontaneous chromosome aberration compared to other types of FA [5, 6]. Heterozygous mutations in BRCA2 are associated with hereditary breast and ovarian cancer [7].</td>
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<tr>
<td>BRIP1 (FANCJ)</td>
<td>FA complementation group J is associated with biallelic mutations in the BRIP1 gene [8]. There is some evidence that heterozygous BRIP1 mutations may be associated with increased breast cancer susceptibility [9].</td>
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<tr>
<td>ERCC4 (FANCO)</td>
<td>FA complementation group Q is associated with biallelic ERCC4 mutations [10]. ERCC4 mutations can also be associated with xeroderma pigmentosa [11].</td>
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<tr>
<td>FANCC</td>
<td>Biallelic FANCA mutations are associated with FA complementation group A [12]. Patients with mutations associated with no FANCA protein production may have earlier onset anemia and higher risk of leukemia, compared with patients with production of an abnormal FANCA protein [12].</td>
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<tr>
<td>FANCB</td>
<td>Mutations in the X-linked FANCB are associated with FA complementation group B. Affected patients typically have multiple malformations, including a ventriculomegaly or hydrocephalus, bilateral radial defects, vertebral defects, and renal agenesis [13]. An estimated 50% of affected males do not survive the perinatal period; heterozygous females are typically unaffected and exhibit skewed X-inactivation [13].</td>
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<tr>
<td>FANCC</td>
<td>FA complementation group C is associated with biallelic mutations in FANCC. A founder mutation in FANCC exists in the Ashkenazi Jewish population, and has a carrier frequency of 1 in 100 [14].</td>
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<tr>
<td>FANCD2</td>
<td>Biallelic mutations in FANCD2 are associated with FA complementation group D2, and account for approximately 3-6% of all cases of FA [15]. Patients with FANCD2 mutations frequently have congenital malformations, and have earlier onset hematological manifestations compared FA cases overall [15].</td>
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<tr>
<td>FANCE</td>
<td>Homozygous mutations in FANCE have previously been identified in 2 Turkish patients and 1 Bangladeshi patient with FA complementation group E [16].</td>
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<tr>
<td>FANCF</td>
<td>FA complementation group F is caused by homozygous or compound heterozygous mutations in the FANCF gene [17].</td>
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<tr>
<td>FANCG</td>
<td>Biallelic FANCG mutations are associated with FA complementation group G. FANCG mutations are typically associated with more severe cytopenia and a higher risk of leukemia than is observed with cases of FA in general [12].</td>
</tr>
</tbody>
</table>
Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Fanconi Anemia Sequencing Panel (sequence analysis of 18 genes)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube. NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.
Cost: $2000
CPT codes: 81407
Turn-around time: 8 weeks
Note: We cannot bill insurance for the Fanconi Anemia Sequencing panel

Fanconi Anemia Deletion/Duplication Panel (deletion/duplication analysis of 17 genes)
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube. NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.
Cost: $1545
CPT codes: 81406
Turn-around time: 4-6 weeks

Results:
Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Fanconi Anemia Sequencing Panel. All abnormal results are reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu. You can also contact us at 773-834-0555 or ucgslabs@genetics.uchicago.edu

References:

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS