



**Next Generation Sequencing Panel for Fanconi Anemia**

**Clinical Features:**

Fanconi anemia (FA) is a chromosomal instability disorder associated 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 first 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					
<b>BRCA1(FANCS)</b>	<b>BRCA2 (FANCD1)</b>	<b>BRIP1 (FANCI)</b>	<b>ERCC4 (FANCC)</b>	<b>FANCA</b>	<b>FANCB</b>
<b>FANCC</b>	<b>FANCD2</b>	<b>FANCE</b>	<b>FANCF</b>	<b>FANCG</b>	<b>FANCI</b>
<b>FANCL</b>	<b>PALB2 (FANCN)</b>	<b>RAD51 (FANCR)</b>	<b>RAD51C (FANCO)</b>	<b>UBE2T(FANCT)</b>	<b>SLX4 (FANCP)</b>

Gene	Clinical Features
BRCA1 (FANCS)	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].
BRCA2 (FANCD1)	Homozygous or compound heterozygous mutations in <i>BRCA2</i> are associated with FA complementation group D1. <i>BRCA2</i> 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 <i>BRCA2</i> are associated with hereditary breast and ovarian cancer [7].
BRIP1 (FANCI)	FA complementation group J is associated with biallelic mutations in the <i>BRIP1</i> gene [8]. There is some evidence that heterozygous BRIP1 mutations may be associated with increased breast cancer susceptibility [9].
ERCC4 (FANCC)	FA complementation group Q is associated with biallelic <i>ERCC4</i> mutations [10]. <i>ERCC4</i> mutations can also be associated with xeroderma pigmentosa [11].
FANCA	Biallelic <i>FANCA</i> 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].
FANCB	Mutations in the X-linked <i>FANCB</i> 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].
FANCC	FA complementation group C is associated with biallelic mutations in <i>FANCC</i> . A founder mutation in <i>FANCC</i> exists in the Ashkenazi Jewish population, and has a carrier frequency of 1 in 100 [14].
FANCD2	Biallelic mutations in <i>FANCD2</i> are associated with FA complementation group D2, and account for approximately 3-6% of all cases of FA [15]. Patients with <i>FANCD2</i> mutations frequently have congenital malformations, and have earlier onset hematological manifestations compared FA cases overall [15].
FANCE	Homozygous mutations in <i>FANCE</i> have previously been identified in 2 Turkish patients and 1 Bangladeshi patient with FA complementation group E [16].
FANCF	FA complementation group F is caused by homozygous or compound heterozygous mutations in the <i>FANCF</i> gene [17].
FANCG	Biallelic <i>FANCG</i> mutations are associated with FA complementation group G. <i>FANCG</i> mutations are typically associated with more severe cytopenia and a higher risk of leukemia than is observed with cases of FA in general [12].

FANCI	FA complementation group I is caused by homozygous or compound heterozygous mutations in the <i>FANCI</i> gene [18].
FANCL	A patient with FA complementation group L and compound heterozygous mutations in <i>FANCL</i> has previously been described [19].
PALB2 (FANCN)	FA complementation group N has been associated with compound heterozygous mutations in <i>PALB2</i> . Heterozygous mutations in <i>PALB2</i> have been associated with increased susceptibility to breast cancer [20].
RAD51 (FANCR)	Wang <i>et al.</i> (2015) identified a novel heterozygous mutation in <i>RAD51</i> in a patient with a FA-like phenotype [21].
RAD51C (FANCO)	A homozygous mutation in <i>RAD51C</i> has previously been described in a family with FA complementation group O [22]. Heterozygous mutations in this gene have been associated with breast cancer predisposition [23].
UBE2T (FANCT)	Two unrelated individuals were reported with biallelic <i>UBE2T</i> missense mutations that rendered the UBE2T protein unable to interact with FANCL and caused Fanconi anemia [24].
SLX4 (FANCP)	FA complementation group P has been associated with either homozygous or compound heterozygous mutations in the <i>SLX4</i> gene [25].

### 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 to 10 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 to 10 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](http://dnatesting.uchicago.edu). You can also contact us at 773-834-0555 or [ucgslabs@genetics.uchicago.edu](mailto:ucgslabs@genetics.uchicago.edu)**

### References:

1. Khincha, P.P. and S.A. Savage, *Genomic characterization of the inherited bone marrow failure syndromes*. *Semin Hematol*, 2013. **50**(4): p. 333-47.
2. Chirmomas, S.D. and G.M. Kupfer, *The inherited bone marrow failure syndromes*. *Pediatr Clin North Am*, 2013. **60**(6): p. 1291-310.
3. Sawyer, S.L., et al., *Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype*. *Cancer Discov*, 2015. **5**(2): p. 135-42.
4. Domchek, S.M., et al., *Biallelic deleterious BRCA1 mutations in a woman with early-onset ovarian cancer*. *Cancer Discov*, 2013. **3**(4): p. 399-405.
5. Hirsch, B., et al., *Association of biallelic BRCA2/FANCD1 mutations with spontaneous chromosomal instability and solid tumors of childhood*. *Blood*, 2004. **103**(7): p. 2554-9.

6. Wagner, J.E., et al., *Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia*. *Blood*, 2004. **103**(8): p. 3226-9.
7. Martin, A.M., et al., *Germline mutations in BRCA1 and BRCA2 in breast-ovarian families from a breast cancer risk evaluation clinic*. *J Clin Oncol*, 2001. **19**(8): p. 2247-53.
8. Levitus, M., et al., *The DNA helicase BRIP1 is defective in Fanconi anemia complementation group*. *J. Nat Genet*, 2005. **37**(9): p. 934-5.
9. Seal, S., et al., *Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles*. *Nat Genet*, 2006. **38**(11): p. 1239-41.
10. Bogliolo, M., et al., *Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia*. *Am J Hum Genet*, 2013. **92**(5): p. 800-6.
11. Cleaver, J.E., et al., *A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy*. *Hum Mutat*, 1999. **14**(1): p. 9-22.
12. Faivre, L., et al., *Association of complementation group and mutation type with clinical outcome in fanconi anemia*. *European Fanconi Anemia Research Group*. *Blood*, 2000. **96**(13): p. 4064-70.
13. McCauley, J., et al., *X-linked VACTERL with hydrocephalus syndrome: further delineation of the phenotype caused by FANCB mutations*. *Am J Med Genet A*, 2011. **155A**(10): p. 2370-80.
14. Kutler, D.I. and A.D. Auerbach, *Fanconi anemia in Ashkenazi Jews*. *Fam Cancer*, 2004. **3**(3-4): p. 241-8.
15. Kalb, R., et al., *Hypomorphic mutations in the gene encoding a key Fanconi anemia protein, FANCD2, sustain a significant group of FA-D2 patients with severe phenotype*. *Am J Hum Genet*, 2007. **80**(5): p. 895-910.
16. de Winter, J.P., et al., *Isolation of a cDNA representing the Fanconi anemia complementation group E gene*. *Am J Hum Genet*, 2000. **67**(5): p. 1306-8.
17. de Winter, J.P., et al., *The Fanconi anaemia gene FANCF encodes a novel protein with homology to ROM*. *Nat Genet*, 2000. **24**(1): p. 15-6.
18. Dorsman, J.C., et al., *Identification of the Fanconi anemia complementation group I gene, FANCI*. *Cell Oncol*, 2007. **29**(3): p. 211-8.
19. Ali, A.M., et al., *Identification and characterization of mutations in FANCL gene: a second case of Fanconi anemia belonging to FA-L complementation group*. *Hum Mutat*, 2009. **30**(7): p. E761-70.
20. Poupouridou, N. and C. Kroupis, *Hereditary breast cancer: beyond BRCA genetic analysis; PALB2 emerges*. *Clin Chem Lab Med*, 2012. **50**(3): p. 423-34.
21. Wang, A.T., et al., *A Dominant Mutation in Human RAD51 Reveals Its Function in DNA Interstrand Crosslink Repair Independent of Homologous Recombination*. *Mol Cell*, 2015. **59**(3): p. 478-90.
22. Vaz, F., et al., *Mutation of the RAD51C gene in a Fanconi anemia-like disorder*. *Nat Genet*, 2010. **42**(5): p. 406-9.
23. Golmard, L., et al., *Germline mutation in the RAD51B gene confers predisposition to breast cancer*. *BMC Cancer*, 2013. **13**: p. 484.
24. Hira, A., et al., *Mutations in the gene encoding the E2 conjugating enzyme UBE2T cause Fanconi anemia*. *Am J Hum Genet*, 2015. **96**(6): p. 1001-7.
25. Stoepker, C., et al., *SLX4, a coordinator of structure-specific endonucleases, is mutated in a new Fanconi anemia subtype*. *Nat Genet*, 2011. **43**(2): p. 138-41.

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