

Chapter 20: Clinical Management Checklist

Introduction

Fanconi anemia (FA) is a complex disease that can affect all systems of the body. Patients are at risk for bone marrow failure, leukemia, squamous cell carcinoma, and other types of malignancies. In addition, patients can be affected by other facets of the disease, such as abnormalities of the endocrine, gastrointestinal, and skeletal systems.

This checklist, a compendium of suggestions from many authors of the FA Guidelines, is not all-inclusive and should not take the place of reading the comprehensive information provided in this book. Many of the tests and procedures mentioned in this chapter will not be appropriate for every individual patient, nor does the following checklist present an exhaustive list of possible tests or treatments that each FA patient could or should undergo. Rather, this checklist should be used at the discretion of the patient's physician and should be tailored to the needs of the individual patient and his or her family.

Diagnostic Testing for FA

Who should be tested? (detailed in *Chapter 1*)

- All children with multiple anatomic abnormalities, possible VACTERL syndrome (birth anomalies affecting several parts of the body that tend to occur together), very short stature, or abnormal thumbs should be tested for FA.
- All full siblings of the FA patient, regardless of whether they show physical signs or symptoms, must be tested to rule out FA and to determine whether they are matched sibling donors for stem cell transplantation.
- All children of individuals with FA.
- Young adults that present at atypical ages for specific malignancies, including squamous cell carcinomas of the head and neck or vulva.

- Individuals with excessive toxicity after treatment with alkylator chemotherapeutics, especially if for an FA-related malignancy such as myeloid leukemia or squamous cell carcinoma of the head and neck.

How are patients tested for FA? (detailed in *Chapters 1-2*)

- Anyone suspected of having FA should be referred to a doctor who specializes in diseases of the blood, known as a hematologist, to arrange for a diepoxybutane (DEB) or mitomycin C (MMC) chromosome fragility test of blood lymphocytes. In the US, this test should be performed at a clinically certified (CLIA) laboratory that has expertise in FA diagnostic testing. Testing can also be performed by analyzing cell cycle arrest using flow cytometry after exposure to a crosslinker, as is used in Germany for the initial testing. The Fanconi Anemia Research Fund (FARF), the United States-based organization that published this book, maintains a website (www.fanconi.org) with a list of such testing centers.
- If diagnostic test results of blood are not conclusive and there is a high probability of FA based on clinical assessment, skin fibroblasts should be obtained for more complete testing. If the result remains inconclusive, additional diagnostic testing is available, albeit predominantly available through FA Comprehensive Care Centers, and is further described in *Chapter 2*.

Good to Know

Chromosomes are strands of genetic material that are passed down from parents to children. Most humans have 23 pairs of chromosomes, including 1 pair of sex chromosomes (females have two 'x' sex chromosomes; males have one 'x' and one 'y' sex chromosome).

Diepoxybutane and mitomycin C are chemicals used to break chromosomes in what is called a **chromosome fragility test**.

Flow cytometry is a tool used to study the number and types of cells present in a patient's blood sample.

After an FA Diagnosis: What's Next?

Good to Know

A **cytogenetic evaluation** examines parts of the patient's cells, including chromosomes.

Renal dysplasia refers to abnormal formation of the kidney, along with irregular cysts.

Hydronephrosis, or swelling of the kidneys, occurs when urine accumulates and is unable to make its way out of the kidneys.

Medical management after diagnosis

The care of most patients should be coordinated by a hematologist with expertise in FA, in conjunction with the patient's local physician. See *Chapter 3* for a thorough discussion of ongoing hematological care.

Complete history and physical

Patients diagnosed with FA should undergo a complete laboratory work up and physical examination that includes the following components:

- **Family history:** Assess consanguinity and history of prior family members with anemia, physical abnormalities, or cancer.
- **Past medical history:** Assess prior blood counts, congenital (present at birth) malformations, prior surgery, and medications previously used.
- **Hematologic (blood) assessment:** Determine the patient's complete blood count and differential, and perform a bone marrow aspiration, biopsy, and cytogenetic evaluation.
- **Hepatic (liver) assessment:** Assess liver enzymes and total bilirubin.
- **Renal (kidney) assessment:** Assess serum electrolytes and creatinine, and perform ultrasound to rule out renal dysplasia, hydronephrosis, and anomalies of the bladder and related areas.
- **Urologic examination:** Assess for external structural abnormalities, genitourinary (GU) reflux, urinary tract infections, and GU malformations. If a renal abnormality is found in a female, the patient should be assessed for reproductive tract malformations.

- **Endocrine (growth and hormone) evaluation:** Assess thyroid function, growth hormone parameters, serum glucose and/or glucose tolerance, lipid assessment, and bone mineral density.
- **Ear and hearing examination:** This exam should be performed by an otolaryngologist (an ear, nose, and throat specialist) to assess for hearing loss and/or structural abnormalities of the ears.
- **Eye examination:** This exam should be performed by an ophthalmologist, a type of eye doctor, if clinically indicated.
- **Examination for head and neck cancer:** This exam should be performed by an otolaryngologist.
- **Gynecological (reproductive) examination:** This exam should be performed by a gynecologist and is recommended for female patients aged 13 (external exam only) and 18 (comprehensive exam) and older. Age as well as menstrual and sexual history will dictate the specifics of the examination. See the *Reproductive Tract* section below for more detail. In addition, the physician should check for reproductive tract anomalies if the patient is known to have kidney anomalies.
- **Examinations by other specialists:** The nature of these exams will depend on the individual needs of the patient.

Genetic counseling (detailed in Chapter 17)

Upon diagnosis, the patient and family should be referred to a genetic counselor who can explain the genetic testing process, clarify the mode of inheritance of FA, and provide reproductive and, if applicable, cancer counseling.

Complementation group assignment (detailed in Chapter 2)

Identification of the FA complementation group and the underlying FA gene defects can guide the patient's medical management and help assess the patient's cancer risk. In the past, complementation group analysis was predominantly performed by FA-specialized laboratories, followed by screening of the FA gene. In the near future, this initial testing will be replaced by high-throughput sequencing approaches that are capable of identifying most genetic defects in patients with FA. When the underlying defect(s) cannot be identified by this approach, or in countries where this technology is not available, retroviral complementation testing, FANCD2 western blotting, or candidate gene sequencing remain viable approaches to further classify patients with FA as described in *Chapter 2*.

Mutation analysis (detailed in Chapter 2)

Mutation analysis—a test to determine a patient’s genetic abnormalities—is available at specialized diagnostic laboratories and can be used to determine or confirm the initial complementation group result. This type of analysis is also used to perform other genetic tests, such as carrier testing or prenatal testing. It can guide family planning efforts, and may prove important for determining whether a patient is eligible to participate in prospective gene therapy trials or other research studies.

Prenatal testing and preimplantation genetic diagnosis (detailed in Chapter 17)

Families wishing to have additional children may be interested in pursuing prenatal or preimplantation genetic diagnosis. Prenatal testing may be performed by amniocentesis or CVS and can be done with a chromosomal breakage test. Before pre-implantation genetic diagnosis can be performed, the mutations(s) in the patient’s FA gene must be identified. The physician should refer such families for appropriate medical and genetic counseling.

Living with FA: General Challenges

Good to Know

Acute myelogenous leukemia (AML) is a cancer of the blood and bone marrow.

Blood cells are made in **bone marrow**, the spongy material inside bones.

Cytopenia refers to an abnormally low number of blood cells.

Graft-versus-host disease (GvHD) is a complication that can occur after a bone marrow transplant, when immune cells in the transplanted material consider the patient “foreign” and attack the patient’s body.

Myelodysplastic syndrome (MDS) refers to a diverse group of bone marrow disorders where the blood stem cells are abnormal and are unable to produce healthy blood cells. Formerly known as “preleukemia.”

Polypharmacy: A warning about potential drug interactions

The involvement of multiple subspecialists introduces the risk that medications prescribed by one physician will interact adversely with those prescribed by another or that the use of non-prescription drugs may interact adversely with prescribed medication. It is extremely important that all subspecialists communicate with the primary physician to coordinate care. The patient should

take care to share with the primary physician and subspecialists all prescription and non-prescription drugs, dietary supplements and homeopathic agents used.

Cancer screening

Patients with FA are at extraordinary risk for developing cancer at an early age, and therefore require lifelong surveillance, regardless of whether they have undergone a bone marrow transplant. See specific recommendations by organ site below in the section entitled *Living with FA: Body Site-Specific Concerns*.

Radiation exposure

Because patients with FA have increased sensitivity to radiation (depending in part on the affected FA gene), the primary physician involved in managing the patient should work with the patient's family and all of the patient's care providers to reduce exposure to diagnostic radiation as much as possible.

Bone marrow failure (detailed in *Chapter 3*)

Most patients with FA develop bone marrow failure, however, the age of onset can be highly variable, even among affected siblings. All patients should be monitored by a hematologist with experience in FA, regardless of whether they have bone marrow involvement. A detailed schematic for clinical monitoring of bone marrow failure is found in *Chapter 3*.

Good to Know

Stem cells: Cells that can develop into one of many types of specialized cells in the body.

Hematopoietic stem cell transplantation (HSCT): A medical procedure that destroys the stem cells in a patient's bone marrow and replaces them with stem cells from a donor's bone marrow.

Human leukocyte antigen (HLA): A protein found on the surface of cells in the body, this protein helps the body determine what is "self" and what is "foreign." An HLA-matched donor increases the chances that the patient's body will accept the transplant as "self."

- **Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML).** Patients with FA are at high risk of developing MDS and AML. They should be monitored closely to assess possible onset of MDS or frank leukemia, and to identify the presence of cytogenetic abnormalities that may warrant immediate intervention. Bone marrow aspiration, with or without biopsy, and cytogenetic evaluation should be done annually in patients with FA who have not received a stem cell transplant to allow comparison of the patient's current marrow to previous specimens. See *Chapter 11* for an individualized schedule for clinical monitoring of bone marrow and timing of referral for discussion with a transplant center.
- **HLA typing.** Early high-resolution HLA typing of the patient and immediate family members is recommended to assess the availability of potential bone marrow donors, should a transplant be necessary. A transplant physician can then decide whether there is a suitable family donor and/or make reasonable estimates of the time required to find a donor in the unrelated donor registries based on the HLA-typing. *In general, however, to ensure prompt and effective medical care, a donor search (if the patient has no sibling donor) should be initiated at least 4 months before the need for transplant and long before the development of MDS or AML.*

Hematopoietic stem cell transplantation (detailed in Chapters 11 and 12)

Hematopoietic stem cell transplantation (HSCT) is currently the only therapy available to cure patients with FA of marrow aplasia, prevent progression to MDS or AML, and cure existing MDS or AML.

- **Pre-transplant precautions in patients with FA.** The FA diagnosis must be confirmed before proceeding to transplant. The donor, if related to the patient, must be tested to rule out the possibility of FA. The physician should take ample time to discuss childbearing options with the patient and family before transplant, as the transplant may affect future fertility.
- **Selecting a transplant center.** Because transplants in patients with FA are so complex, the physicians who developed these guidelines feel strongly that if a local transplant center has performed fewer than 10 transplants in patients with FA, the patient should be referred to a transplant center with greater experience in FA transplants whenever possible.

Post-Transplant Care
<p>Schedule of post-transplant clinical examinations See Table 2 in <i>Chapter 12</i> for a schedule of the clinical examinations needed after transplant.</p>
<p>Early complications</p> <ul style="list-style-type: none"> • Watch for early complications of transplant, such as GvHD, graft failure, organ toxicity, and infections. Provide close follow-up of rashes, diarrhea, liver enzymes, and blood counts, with testing for viruses and monitoring of drug levels.
<p>Late complications</p> <ul style="list-style-type: none"> • Monitor for chronic GvHD, organ toxicity (cardiac, pulmonary, renal) or endocrinopathies (diabetes, hypothyroidism, gonadal dysfunction), osteoporosis, avascular necrosis, and cancer, particularly HNSCC and anogenital SSC.
<p>Prophylaxis to prevent infectious disease (yeast/fungal, viral, or protozoal infections)</p> <ul style="list-style-type: none"> • Most transplant centers will expect the patient to remain near the facility for a minimum of 100 days, during which time the patient is at highest risk for developing immunologic complications (i.e., graft rejection, GvHD, and opportunistic infections) associated with transplantation. Prophylactic antibiotic regimens commonly used after HSCT are outlined in <i>Chapter 12</i>.
<p>Immune reconstitution and immunizations after transplant</p> <ul style="list-style-type: none"> • The patient should be screened for immune reconstitution 1 year after transplant. • The primary care physician should discuss the exact timing of immunizations with the patient's transplant physician. • All patients and their family household members should receive the influenza vaccine on an annual basis. Only the intramuscular formulation should be administered because intranasal influenza vaccine contains live virus, which puts the patient at risk of becoming ill.
<p>Hematology follow-up care</p> <ul style="list-style-type: none"> • After transplantation, the patient's transplant physician will determine how often blood counts and bone marrow (BM) tests are needed. • In general, BM aspirates and biopsies are performed several times during the first year after transplant. The pattern thereafter varies widely by transplant center. • Subsequent BM examinations are warranted if the patient has mixed chimerism, remains transfusion dependent, or if there are concerns about low peripheral blood counts.
<p>Ophthalmology follow-up care</p> <ul style="list-style-type: none"> • The three major ocular complications after transplantation are cataracts, dry eyes (usually associated with GvHD), and retinopathy. • Any change in visual acuity should be assessed immediately.

Blood transfusions and iron overload

- **Transfusions.** Transfusion may adversely affect transplant outcomes and should be avoided if possible. If transfusions are essential, blood products should be cytomegalovirus (CMV)-safe and irradiated. Family members should not be used as blood donors for the patient. Timely consideration of transplant is recommended if regular transfusions are required.
- **Iron overload.** Patients who receive multiple transfusions of red blood cells are at risk for accumulating toxic levels of iron. The liver, heart, and endocrine organs are primary sites of iron accumulation, and end-organ damage may result (e.g., hepatic cirrhosis, heart failure, endocrine dysfunction). For an extensive discussion of the management of iron overload, refer to *Chapter 3*. Referral to a pediatric gastroenterologist or hematologist with expertise in iron toxicity is indicated for monitoring of iron overload.

Novel treatments (detailed in *Chapter 13*)

- If the patient does not qualify for currently available treatment for FA, the patient or family should contact a major medical facility with a Fanconi anemia comprehensive care center to determine if and where novel treatments may be available on a clinical trial basis.
- In addition, the Director of Family Support Services at FARF can assist patients and families in locating possible clinical trials.

Living with FA: Body Site-Specific Concerns

Bone health (detailed in *Chapter 6 and 7*)

The relative risk of low bone density in FA patients remains controversial. However, a stem cell transplant may increase the risk of osteopenia, or reduced bone mass, for any patient regardless of underlying diagnosis. The recommendation for pre-transplant patients is to obtain a bone density screening (DXA scan) at age 14, with follow-up as needed. For patients who have undergone a transplant, a DXA scan should be obtained 1 year post-transplant, with ongoing monitoring as needed. Independent of transplantation, premature menopause is a high-risk factor for osteoporosis/osteopenia and gynecological experts who treat adult women with FA recommend careful monitoring of bone health. Long-term treatment with corticosteroids also increases the risk of osteoporosis/osteopenia. Recent studies suggest that FA men as well as women may be at risk.

Ears and hearing (detailed in *Chapter 8*)

Patients with FA should be examined by an otolaryngologist at diagnosis to assess for possible hearing loss or structural abnormalities of the eardrums and/or middle ear bones. If the patient has structural abnormalities, the otolaryngologist may consider possible surgical intervention to improve hearing.

An audiologist should assess the patient at the time of diagnosis to determine whether an amplification system would be useful if hearing loss is documented. These systems can be used for children as young as 4 months. The audiologist can help the family arrange for speech and language therapy, if needed, and should also contact the patient's school district to inquire about early intervention services (as provided in the US from birth through age 21 by the Individuals with Disabilities Education Act).

If a patient with FA receives potentially ototoxic drugs (i.e., that can impair hearing), such as certain intravenous antibiotics, iron-chelating agents, and/or chemotherapy drugs used during hematopoietic stem cell transplant, the patient's auditory function should be monitored with serial audiograms.

Digestive tract (detailed in *Chapter 4*)

Patients with gastrointestinal or hepatic concerns should be seen by a gastroenterologist. A number of people with FA have gastrointestinal symptoms, such as poor oral intake, nausea, abdominal pain, and/or diarrhea. *These problems may affect nutrition and/or quality of life in patients with FA.* The physician should ask the patient and family about gastrointestinal symptoms during routine clinic visits, as patients do not often disclose these concerns voluntarily.

The hepatic complications of androgens are also a concern in patients with FA. Androgens, which may be used to treat low blood counts in FA, are associated with multiple hepatic complications. Liver enzymes should be monitored every 3-6 months in patients receiving androgens, and a liver ultrasound every 6-12 months is recommended.

Good to Know

Osteopenia refers to reduced bone mass. **Osteoporosis**, a more serious condition, refers to brittle bones that are easily broken.

An **oral glucose tolerance test** measures the body's ability to regulate blood sugar. This test can help determine if a patient has pre-diabetes or diabetes.

A **radial ray** defect is a birth anomaly affecting bones in the hand.

Growth and hormones (detailed in Chapter 7)

Many children and adults with FA have endocrine problems, including growth hormone deficiency, hypothyroidism, pubertal delay, or diabetes. To ensure optimal care, the patient should consult with an endocrinologist or pediatric endocrinologist—a doctor with experience in growth and puberty—as well as other sub-specialists as indicated.

- **Baseline and ongoing evaluation.** At diagnosis and annually, each FA patient should receive a thorough baseline endocrine evaluation.
- **Growth.** Nutritional and medical causes for poor growth should be identified as early as possible for optimal treatment. Growth in children with FA should be followed clinically. Height, determined on a stadiometer, should be plotted on a growth chart at least annually.
- **Puberty.** Onset of puberty should be evaluated by at least annual physical examinations to evaluate stage and progression. After age 12, pubertal hormone concentrations should be obtained at least every 2 years as needed to assess pubertal progression.
- **Glucose tolerance.** A 2-hour oral glucose tolerance test (OGTT) with insulin levels should be obtained and repeated as determined by the endocrinologist.
- **Diet and exercise.** All persons diagnosed with FA, regardless of OGTT results, should take care to engage in regular exercise and consume a healthful diet that provides adequate calories and follows the guidelines of the American Diabetes Association. Concentrated sweets should be avoided.

Hands and arms (detailed in Chapter 5)

Patients with hand or arm abnormalities should be assessed at the time of diagnosis by an orthopedic surgeon with experience in congenital limb anomalies. It is very important that the surgeon hold a *Certificate of*

Added Qualification in Hand Surgery. Early referral of the patient to an orthopedic upper extremity specialist is important to obtain the best possible surgical outcome.

The orthopedic surgeon should consult with the patient's primary physician. The surgeon should provide emotional support to the patient and family by initiating open discussions about the patient's psychological adjustment to the hand or arm anomalies.

Head and neck (detailed in *Chapter 14*)

Patients with FA are at extremely high risk of developing squamous cell carcinoma of the head and neck (HNSCC). Proper prevention, surveillance, and treatment of HNSCC are essential.

Prevention
<ul style="list-style-type: none">• Beginning at age 10, the patient should obtain a thorough examination every 6 months from an otolaryngologist, oral surgeon, or other doctor who is experienced in head and neck cancer detection and is familiar with FA. The exam should include a careful exploration of the nasopharynx, oropharynx, hypopharynx, and larynx.• Maintain good oral hygiene.• Minimize exposures to alcohol—including mouthwashes that contain alcohol—and avoid tobacco use and exposure to second-hand smoke.• Receive the HPV vaccination series, beginning at age 9 for both boys and girls according to the recommendation of pediatric societies worldwide, to possibly prevent squamous cell carcinoma associated with the HPV.
Treatment and surveillance
<ul style="list-style-type: none">• Suspicious lesions should be immediately examined via inspection, brushes, or biopsies. If a premalignant lesion is found, examinations should increase to every 2 to 3 months, at the physician's discretion. Malignant lesions must be treated immediately, as a cure can best be achieved via early surgical removal. Treatment should be discussed with a hematologist/oncologist with experience in FA.• Aggressive monitoring by the surgeon is an absolute must for those already treated for head and neck cancer.

Mouth and teeth (detailed in *Chapter 10*)

All patients with FA should have regular dental examinations at least every 6 months by a dentist who is well versed in FA cancer risks. The examination should include a thorough screening for possible oral cancer.

Special note for post-transplant patients:

Because of the risk of bacteremia, patients should not have dental cleaning, extraction, or other invasive procedures for at least 1 year after transplantation.

Reproductive tract (detailed in *Chapter 6*)

Female patients with FA may experience a variety of gynecologic issues, including structural abnormalities, delayed puberty, decreased fertility, early menopause, and a high risk of squamous cell carcinoma of the lower genital tract, which includes cervical, vaginal, vulvar, and anal cancers.

- **Gynecologic exams.** Beginning at age 13, the patient should have annual examinations by a gynecologist for visual inspection of the external genitalia. By age 18, sexually inactive patients should receive comprehensive annual gynecologic exams with cervical cytology testing (Pap smears), along with a discussion of STDs and contraception. Sexually active women with FA should undergo regular comprehensive exams. A colposcopy and biopsy should be done if lesions are identified during the exam or if the patient's cervical cytology test is abnormal.
- **HPV vaccination.** The patient should obtain a human papillomavirus (HPV) vaccination series beginning at age 9 to prevent HPV infection and potentially mitigate HPV-associated cancers.
- **Reproductive tract anomalies.** The physician should check for reproductive tract anomalies if the patient is known to have kidney anomalies.
- **Breast cancer.** Breast cancer surveillance, including annual breast exams, should begin by the patient's early 20s. Screening mammograms can be initiated by age 25 or if a mass is detected; however, the risks and benefits of mammography and its alternatives must be considered in light of FA cells' hypersensitivity to radiation. See *Chapter 6* for more specific recommendations.
- **Pregnancy.** The physician should discuss childbearing options with female patients before transplant, as the transplant may further affect the patient's future fertility. The patient should not take androgens during pregnancy. While pregnancy for women with FA who have not been transplanted is not life-threatening, it nonetheless may impact onset or severity of bone marrow failure, requiring intensified surveillance. The pregnancy

should be considered high risk and should be co-managed by a maternal/fetal medicine specialist and a hematologist. Pregnancies after stem cell transplantation have occurred, but are rare.

- **Menopause.** Patients with FA usually experience premature menopause. Thus, the physician should consider the patient's risk of post-menopausal conditions such as osteoporosis, cardiovascular disease, breast cancer, and the management of hot flashes.

Skin (detailed in *Chapter 9*)

Patients with suspicious nevi (birthmarks) or other abnormal skin lesions should be examined by a dermatologist. All patients with FA should limit sun exposure and wear sunscreen to reduce the risk of skin cancer. Post-transplant patients should limit sun exposure to reduce the risk of cutaneous chronic GvHD.

Living with FA: Transitioning to Adult Medical Care

Patients with FA are usually diagnosed in childhood, with their medical care managed in the pediatric medical system. As patients reach adulthood, the physician and patient must develop a plan for a seamless transition to adult medical care. This plan should allow for ample time to educate the adolescent patient and his or her family about the transition and to locate appropriate adult medical resources.

Creating an adult medical care plan (detailed in *Chapter 16*)

The adult medical care plan should include surveillance and treatment of all aspects of the disease, including:

- Preventive health care.
- Ongoing hematological evaluation of patients who have received transplants, as specified by the transplant physicians. Patients who have not yet been transplanted should consult with experts in the transplantation of FA adults.
- Continuation of rigorous cancer prevention and surveillance, especially of head and neck and gynecological SCC.
- Screening for vascular and cardiac disease post bone-marrow transplant (electrocardiogram [EKG] and echocardiogram).

- Screening for endocrine-related conditions, such as abnormal thyroid function, diabetes mellitus, reduced fertility, and osteoporosis.
- Screening for effects of treatment that manifest later in life, such as cataracts. Patients receiving transfusions need to be screened for iron overload or the effects of iron-chelation therapy.
- HPV vaccination to help prevent SCC.
- Gynecological consultations to screen for and prevent cancer, to monitor menses, and to manage fertility and menopause issues.

Quality of life in adult patients with FA

Quality of life varies greatly among adult patients with FA. Some may have neurocognitive deficits and need educational, vocational, workplace, community, or interpersonal relationship assistance. At one time or another, patients with FA may experience anxiety, depression, social withdrawal, difficulty with re-entry into society or school after transplant or cancer treatment, and trouble navigating the complex arena of health insurance. Programs to address these needs are available in many communities. Additionally, the Director of Family Support Services for FARF can provide patients and families with assistance in locating resources to address psychosocial or medical issues.

Chapter Committee

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