Molecular Genetic Testing for Osteogenesis Imperfecta (OI)

Purpose: Provide a guide for appropriate evaluation and molecular genetic testing for osteogenesis imperfecta.

Goal:

1. Reduce the risk to the patient:
    a. Decrease unnecessary blood draws
    b. Decrease cost for unnecessary consults and/or testing
    c. Decrease the probability of an incorrect diagnosis
2. Improve value to the patient/family:
    a. Provide the appropriate clinical evaluation for patients with osteogenesis imperfecta
    b. Increase the probability of a correct diagnosis

Description:

Osteogenesis imperfecta is a group of genetic conditions that are characterized by bone fragility, dentinogenesis imperfecta, and later onset hearing loss. The clinical diagnosis depends on the presence of a number of features including fractures (often in the context of minimal to no trauma), short stature often with bony differences, blue sclerae, dentinogenesis imperfecta, progressive hearing loss, ligamentous laxity, positive family history, and specific radiographic (X-ray) findings.

The diagnosis and treatment requires evaluation by specialists familiar with the disorder. Outpatient consultation with the Metabolic Bone Clinic (in Endocrinology) or the Clinical Genetics team should be considered if two or more of the above features are present.

Osteogenesis imperfecta is predominantly autosomal dominant and rarely inherited in an autosomal recessive manner. Multiple genes are associated with features of osteogenesis imperfecta. There are also several additional genetic conditions associated with bone fragility. Because of the complexities involved in interpreting molecular results due to the lack of 100% sensitivity and risk of identifying variants of unknown significance, the use of molecular genetic testing should be reserved for patients who have been evaluated by specialists familiar with the diagnosis. This will reduce the risk of misdiagnosis and misinterpretation of test results.

The diagnosis of osteogenesis imperfecta does not rule out the possibility of non-accidental trauma (NAT). A Metabolic Bone Clinic or Clinical Genetics evaluation and/or molecular genetic testing cannot be used to determine whether non-accidental trauma has occurred. Patients with medical conditions may also experience abuse, and the diagnosis of NAT and osteogenesis imperfecta are not mutually exclusive.*

The SCAN team should be consulted for patients with injuries that are worrisome for NAT. If the SCAN team physician identifies features that suggest a genetic or metabolic bone condition, then that provider can recommend genetic testing (including COL1A1/2 analysis) and can order the testing during an inpatient stay or make a referral to the outpatient Genetic Counseling Clinic to obtain insurance pre-authorization for the testing, counsel the family regarding the complexities of the possible test results, and provide post-test counseling.

Approach to requests:

- Molecular genetic testing for osteogenesis imperfecta will be guided by physical exam, review of family history and diagnostic imaging studies. The diagnosis and treatment of osteogenesis imperfecta requires evaluation by specialists familiar with the disorder. Outpatient consultation with the Metabolic Bone Clinic or Clinical Genetics Clinic should be considered if two or more clinical criteria are present.
- Children with suspected NAT may have genetic or metabolic bone disease that leads to fractures and the Metabolic Bone Clinic will assist the SCAN team in assessing such children.
- Referrals to Metabolic Bone Clinic for children with abuse concerns are accepted only from SCAN team members; the clinic does not accept direct referrals for questions of fractures due to child abuse.
- Seattle Children's laboratory will limit molecular genetic testing for osteogenesis imperfecta to patients who have been evaluated by the SCAN team physicians, Metabolic Bone Clinic, or Clinical Genetics staff, unless molecular genetic testing is determined to be medically necessary in an inpatient case (see Lab Test Stewardship Policy, section B.b. regarding inpatient genetic testing guidelines).
- Families who desire this testing at the recommendation of an attorney or other non-SCH staff are free to seek testing services outside Seattle Children's.

*Important Note:

Consultations to the Metabolic Bone (MBD) Clinic or Clinical Genetics are being requested increasingly in cases with concerns for abusive skeletal injury. These requests come, not only from the SCAN (Safe Child and Adolescent Network) physicians, but also from Child Protective Services (CPS), parents, defense attorneys, and even detectives. Questions are posed whether osteogenesis imperfecta (OI) or other metabolic bone conditions explain the child's injuries instead of abuse.

For evaluations in either the Metabolic Bone Clinic or Clinical Genetics Clinic, the teams should receive appropriate background information and the child's caretakers should have reasonable expectations for the consultation. The role of the clinicians is to render medical opinion on whether the child has any clinical indication to suggest a metabolic bone condition. Only the children who still have a clinical concern for these conditions will be accepted for evaluation and treatment.

Referral Process (for patients with a history of fractures):

1. All referrals to the Metabolic Bone Clinic, when the issue is a concern about child abuse, should be made through SCAN physicians. No direct referrals will be accepted.
    a. Please reference the Child Abuse Consultation Network for Washington State document for phone numbers for the SCAN state-wide physicians.
2. Only those children who have been evaluated by a SCAN physician and are still felt to have a legitimate concern for a disorder of bone fragility will be accepted for Metabolic Bone Clinic evaluation.

3. In making the referral, the SCAN physician will explain to the family the limited role of the Metabolic Bone Clinic.
4. The referral to the Metabolic Bone Clinic should include:
    a. The question being asked of the clinicians
    b. Medical and family history of the patient, including past evaluations and lab results
    c. Past skeletal imaging
    d. Parents/guardians should be encouraged to participate in the consultation (if available) whether the child is in their current care or not.
5. The results of the Metabolic Bone Clinic evaluation shall be provided to the referring SCAN physician, so that the information can be utilized in the SCAN physician's final conclusions.
6. If the SCAN physician has a specific genetic testing plan for a patient with fractures, they will instead refer the patient to the Genetic Counseling Clinic if testing cannot be completed during inpatient/acute hospitalization situations.
7. During inpatient/acute hospitalization situations, consider involving the inpatient genetics team or the endocrinology team for a consult to get support obtaining additional information (possibly including family history, if available). Once the patient is discharged, they can be seen in the Genetic Counseling Clinic or Metabolic Bone Clinic depending on the status of a patient's workup.

Referral Process (for patients with positive family history or clinical features without fractures):

1. If a patient is identified to have a known family history of osteogenesis imperfecta or other metabolic bone condition without fractures that need to be treated, the patient can be seen in the Genetic Counseling Clinic for diagnosis and genetic counseling. The Metabolic Bone Clinic will manage treatment plans.
2. If a patient is identified to have clinical features that raise suspicion for a metabolic bone condition (e.g., blue sclera, dentinogenesis imperfecta), the patient can be seen in the Genetic Counseling Clinic.
3. If a patient has the above, but also has a history of fractures that needs to be managed, then that patient should be referred to the Metabolic Bone Clinic in addition to being referred to the Genetic Counseling Clinic.
4. The referral to the Genetic Counseling Clinic should include:
    a. The question being asked of the clinicians
    b. Medical and family history of the patient, including past evaluations and lab results
    c. Past skeletal imaging
    d. Parents/guardians should be encouraged to participate in the consultation (if available) whether the child is in their current care or not.

References:

GeneReviews: COL1A1/2-Related Osteogenesis Imperfecta. Robert D Steiner, MD, Jessica Adsit, MS, CGC, and Donald Basel, MD. Initial Posting: January 28, 2005; Last Update: February 14, 2013. https://www.ncbi.nlm.nih.gov/books/NBK1295/

Collagen Diagnostics Laboratory, University of Washington: http://uwcpdx.org/collagen-diagnostic-laboratory

Last updated: August 2025