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 disorders 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, short stature often with bone deformity, blue sclerae, dentinogenesis imperfecta, progressive hearing loss, ligamentous laxity, positive family history, and specific X-ray findings. The diagnosis and treatment requires evaluation by specialists familiar with the disorder. Outpatient consultation with the skeletal dysplasia clinic should be considered if two or more criteria 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 Skeletal Dysplasia Clinic evaluation and/or molecular genetic testing cannot be used to determine whether non-accidental trauma has occurred. Patients with medical challenges are at higher risk for abuse. The diagnosis of non-accidental trauma and osteogenesis imperfecta are not mutually exclusive.

Patients considered to be at risk for non-accidental trauma should be referred to the SCAN team. If the SCAN team physician identifies features that suggest a skeletal dysplasia the patient should be referred to the outpatient Skeletal Dysplasia Clinic for evaluation. The experts in the Skeletal Dysplasia Clinic will determine if molecular genetic testing is appropriate, attempt 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 Skeletal Dysplasia 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 Skeletal Dysplasia Clinic will assist the SCAN team in assessing such children.
- Referrals to Skeletal Dysplasia 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 Skeletal Dysplasia Clinic staff in the outpatient clinic, 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.

References:

GeneReview: *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/