Should Patients be Given Research Results?

Blanche P Alter, MD, MPH

Clinical Genetics Branch,
Division of Cancer Epidemiology and Genetics
National Cancer Institute,
Department of Health and Human Services
Bethesda, MD
The Proband

- **Age 10 years:**
  - Aplastic anemia.

- **Age 27 years:**
  - Severe aplastic anemia
  - Early grey hair
  - Nail dystrophy
  - Thin eyelashes
  - Epiphora (watery eyes)
  - Very short telomeres
Previous Treatment

- Age 21 years:
  - Transfusions every 4-6 weeks.

- Age 26 years:
  - Androgens with no apparent benefit.
Father died with aplastic anemia, pulmonary fibrosis, and non Hodgkin’s lymphoma.

Father’s twin died with aplastic anemia.

Cousin has aplastic anemia and abnormal nails.
Pedigree
Dyskeratosis Congenita (DC)

- Age at diagnosis ranges from early childhood to adulthood.
- Inheritance is X-linked, autosomal dominant, and recessive.
- Genes identified so far are *DKC1* and *TERC*; these genes are involved in telomere maintenance.
- DC is rare; there are less than 300 cases reported in the literature.
Diagnosis of DC

- Diagnosis requires 2 of the following 3:
  - Abnormal (dyskeratotic) finger and toe nails
  - Discolored skin (lacey reticular pigmentation)
  - Mucous membrane white patches (leukoplakia)

- DC is also associated with short telomeres.
4 Dyskeratosis Congenita Patients
Clinical Course of DC

- Major complications include aplastic anemia, leukemia, and solid tumors.

- Standard treatment for DC-associated aplastic anemia includes bone marrow transplant (BMT), androgens, or G-CSF +/- Epo.

- Prognosis is poor.
Telomeres and Telomerase

- Telomere - the end of a chromosome

- Telomerase - the enzyme that keeps the telomeres intact during cell division. It has both protein and RNA components.
Flow-FISH Telomere Length

P Lansdorp and G Baerlocher, unpublished

Abnormal = very short = <1%ile
In 2003, the family came to the NIH for participation in an NCI Clinical Genetics Branch protocol, and consultation regarding possible bone marrow transplantation.
4 Siblings

- All siblings have essentially normal physical exams and normal blood counts.
- 3 of the 4 siblings are HLA matches with the proband.
Minor Sibling

- A 13 year old sibling appears to be the best match.

- However, testing at a research laboratory (not CLIA approved) reveals that the 13 year old has very short telomeres.

- The proband does NOT have a mutation in *DKC1* or *TERC*.
Problems - 1

- The implications of the 13 year old sibling’s short telomeres are not clear:
  - Will this child develop DC?
  - Is someone with short telomeres an appropriate bone marrow donor?
Problems - 2

- At the time of signing the assent to receive the results of genetic mutation testing, the 13 year old stated explicitly a preference to not receive genetic mutation results.
  - Did the 13 year old understand the implications of this decision?
  - Does this mean the 13 year old did not want to receive any test results that might reveal a risk for DC?
Questions

- Should the healthy 13 year old be told about having short telomeres?
  - Should the results from a research laboratory be used to select the BMT donor?
  - Should these results be used to guide future clinical care and surveillance for a nonpenetrant family member?
  - How should we interpret the refusal to sign the consent form for disclosure of the results of gene mutation testing?