Should Patients be Given Research Results?

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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

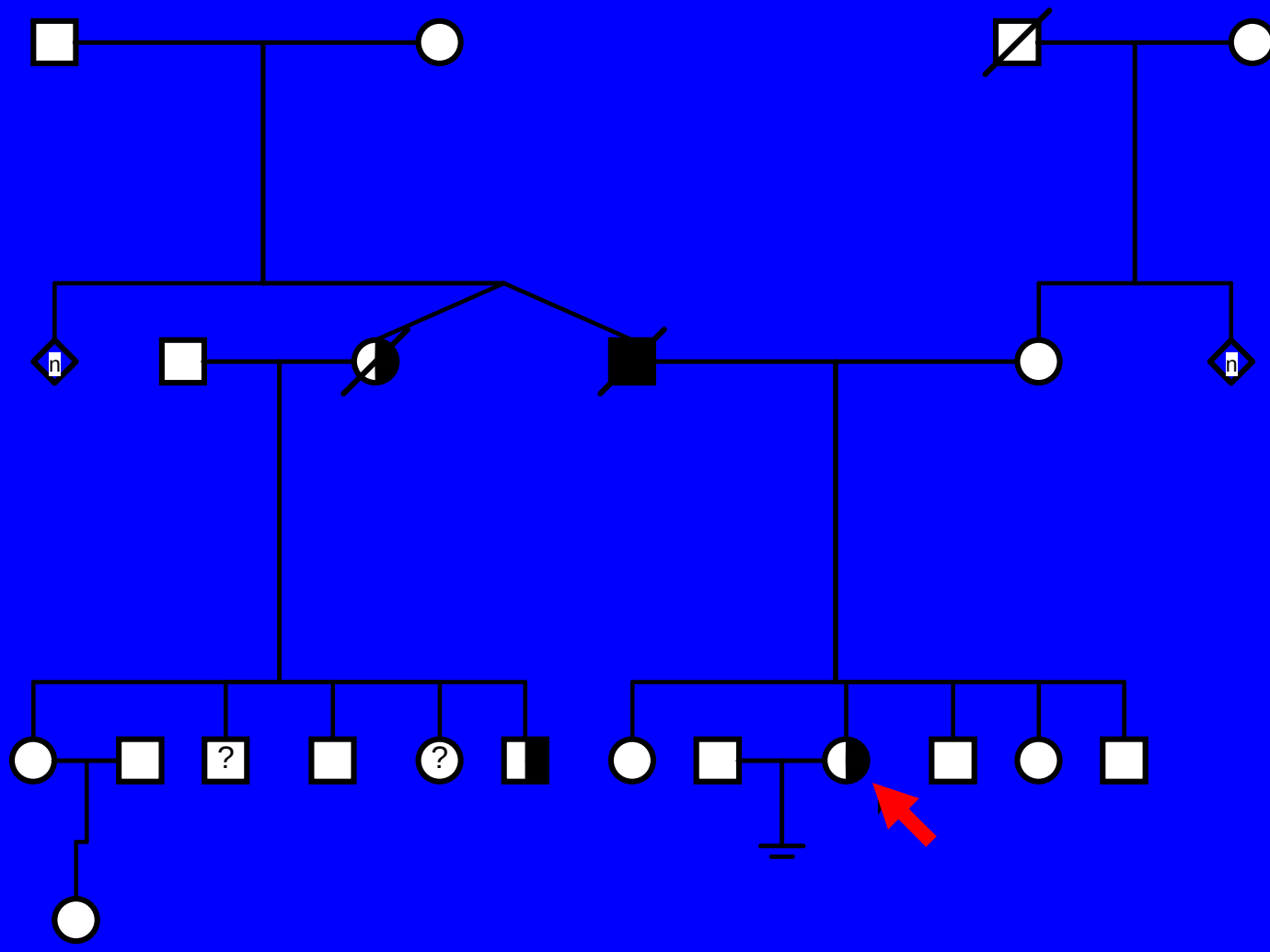
Previous Treatment

- Age 21 years:
  - Transfusions every 4-6 weeks.
- Age 26 years:
  - Androgens with no apparent benefit.

Family History

- 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



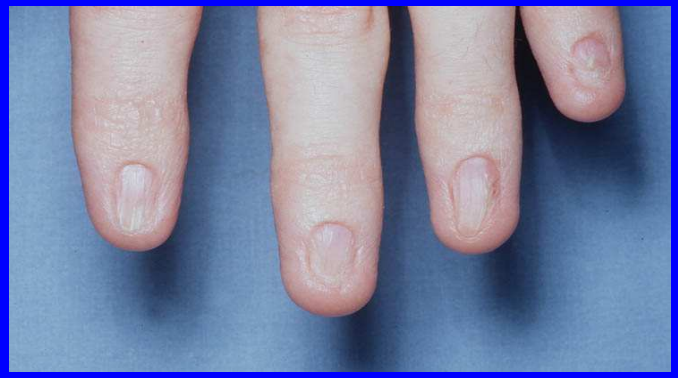
Dyskeratosis Congenita (DC)

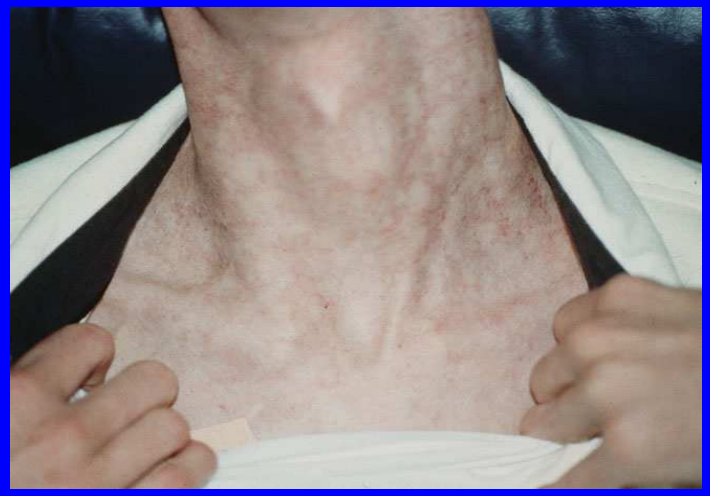
- Age at diagnosis ranges from early childhood to adulthood.
- Inheritance is X-linked, autosomal dominant, and recessive.
- Genes identified so far are *DKC1* and *TERC*; these genes are involved in telomere maintenance
- DC is rare; there are less than 300 cases reported in the literature.

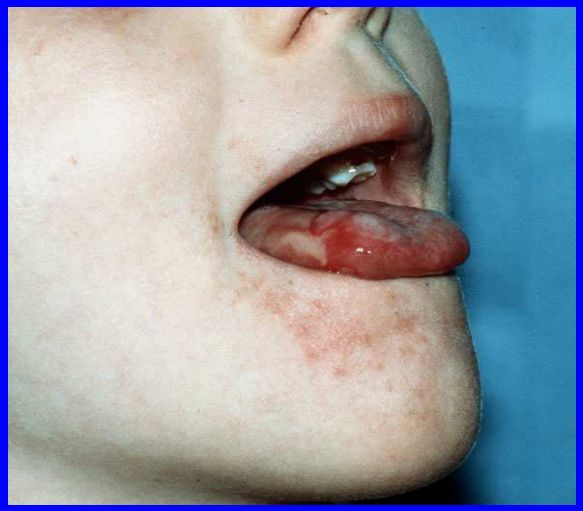
Diagnosis of DC

- 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





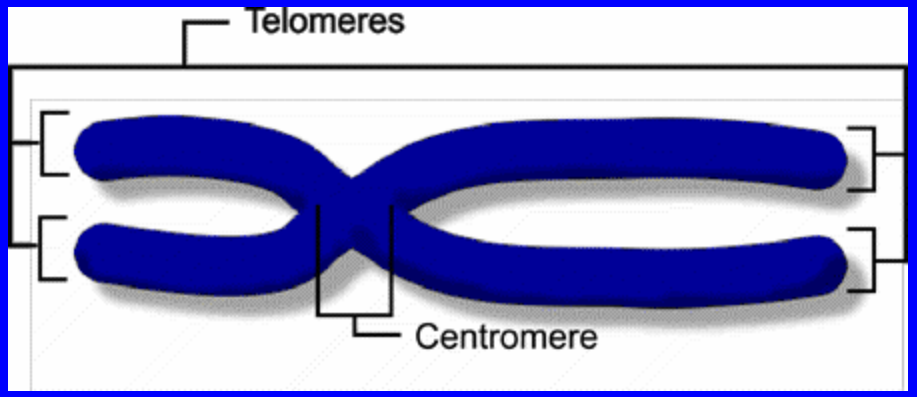


Clinical Course of DC

- 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.

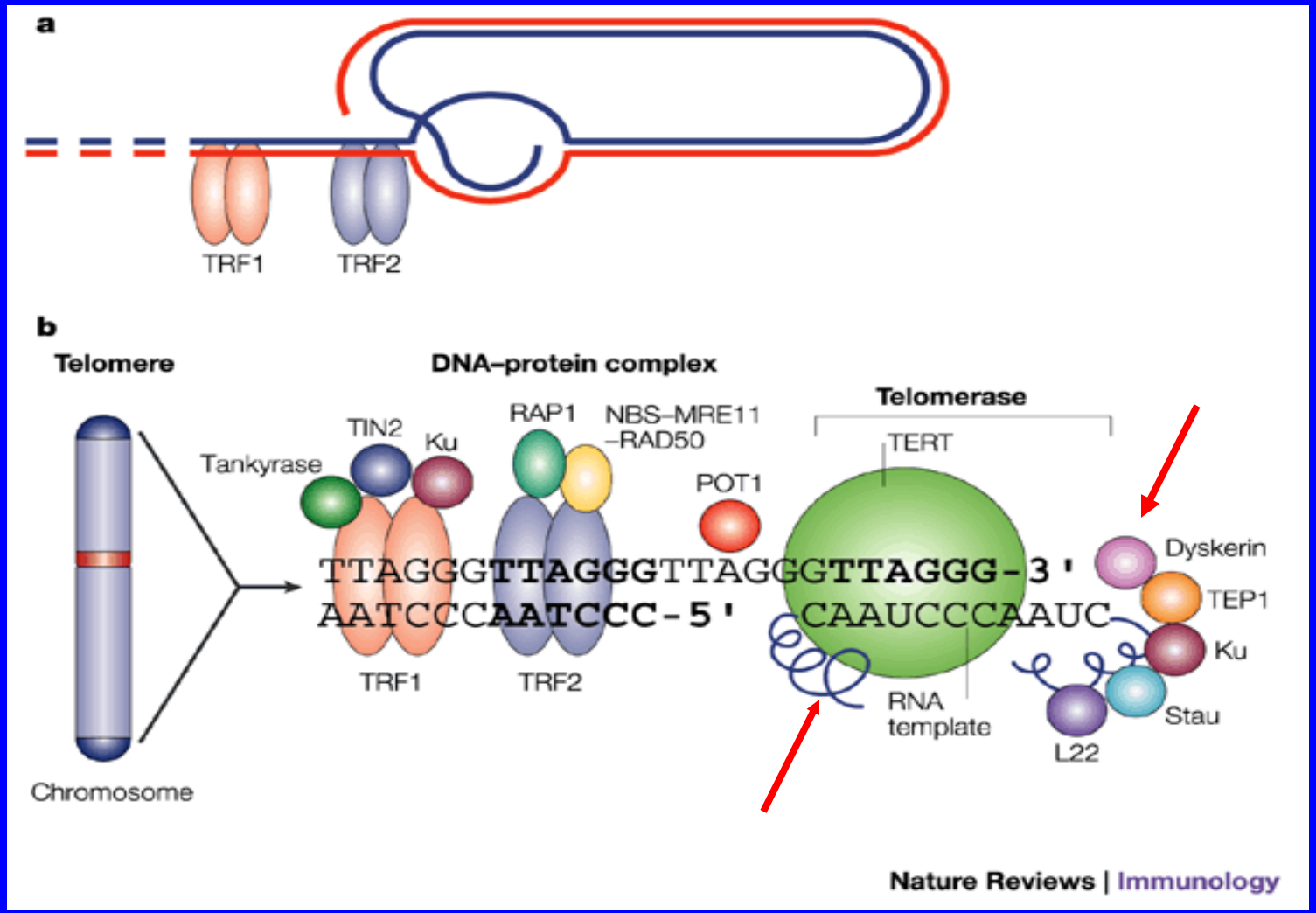
Telomeres and Telomerase

- Telomere - the end of a chromosome

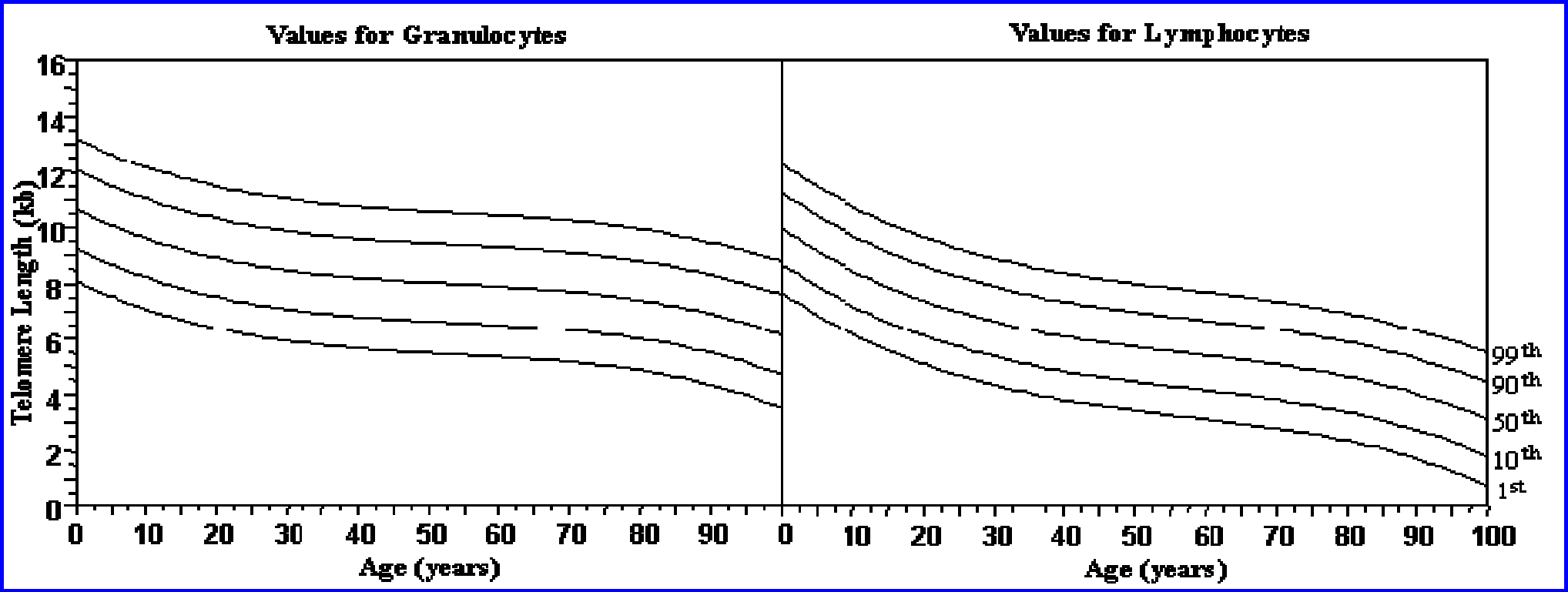


- Telomerase - the enzyme that keeps the telomeres intact during cell division. It has both protein and RNA components.

Telomere Maintenance Pathway



Flow-FISH Telomere Length



P Lansdorp and G Baerlocher, unpublished

Abnormal = very short = <1%ile

NIH

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 <u>any</u> 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?