national neutropenia network
awareness, education, research and support

2022 National Neutropenia Network Virtual Conference:

Congenital Neutropenia

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Dana-Farber Cancer Institute | Boston Children's

Dana-Farber/Boston Children's Cancer and Blood Disorders Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Diagnosis

- Important to confirm diagnosis, since different conditions may be treated and monitored differently
  - Different types of genetic neutropenias are monitored and treated differently
- Diagnostic genetic testing is very helpful

A few words about MDS (Myelodysplastic Syndrome)

- MDS is a pre-leukemic clonal condition
- The definitions of MDS in SCN and other genetic neutropenia conditions are **not** the same as for standard MDS (which is typically a disease of older adults arising out of age-related clonal hematopoiesis).
- Bone marrow transplant is the treatment of choice for MDS in patients with SCN or other genetic neutropenia conditions. This is different from standard approaches for adult MDS. Seek expert consultation!

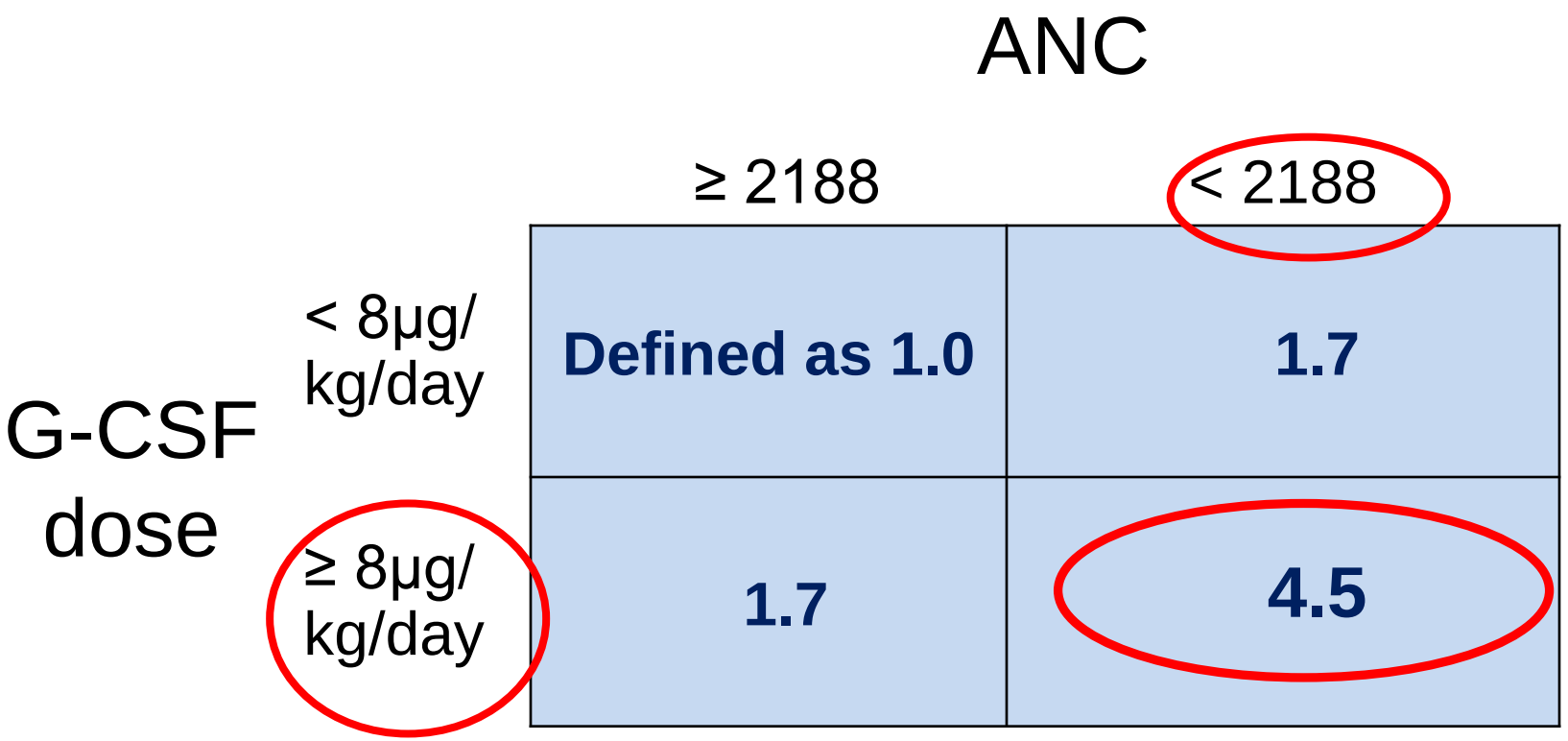
Treatment of Severe Congenital Neutropenia

- G-CSF (filgrastim, Neupogen®, Nivestym, Granix, Zarxio, etc)
  - Increases the neutrophil count
  - For certain conditions (eg: CSF3R germline mutations) or situations, GM-CSF may be appropriate
- Hematopoietic stem cell transplantation
- Investigational:
  - Gene therapy: target the *ELANE* or *SBDS* gene to improve blood cell production
    - blood samples from adults with *ELANE* SCN or *SBDS* mutations needed for studies at Boston Children's Hospital in preparation for clinical trial.
    - **To learn more about this, email: akiko.shimamura@childrens.harvard.edu**
  - Nicotinamide (vitamin B3)
  - Treatments targeting pathways in Shwachman Diamond Syndrome

Monitoring for high risk disease

- Assess clinically (eg infections)
- Assess G-CSF dose and neutrophil response
- Consider outcomes of MDS or AML for specific condition
- Get expert input: word-of-mouth and published studies can be confusing
  - different definitions of MDS (old definitions are no longer considered MDS)
  - lumping together MDS and AML is problematic (they are not the same!)
  - there are new tests available
  - there are new treatments available

Relative Risk of MDS/AML in SCN: G-CSF Response



Rosenberg *et al*., Blood 2006; 107: 4628

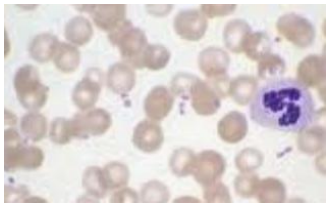
Monitoring for MDS/AML risk

Regular blood counts

- Frequency individualized
- Loss of response to G-CSF
- Decreased red cells or platelets

} Consider bone marrow exam

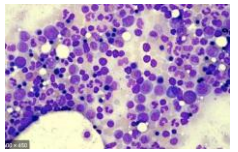
Note: blood count changes are often a late finding that is noted as MDS or leukemia has already developed



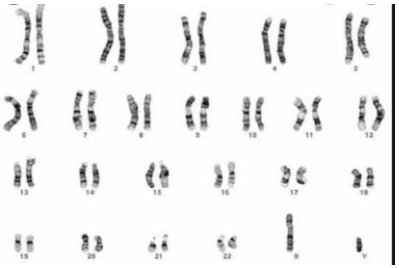
Monitoring for MDS/AML

Yearly bone marrow examination

- Cell number and appearance: look at progression over time.
  - Increasing proportion of cells with dysplasia
  - Dysplasia in a new cell type
  - Rising marrow cellularity with decreasing blood counts

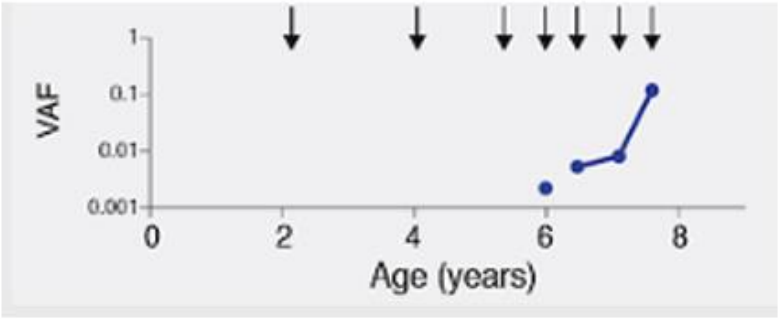


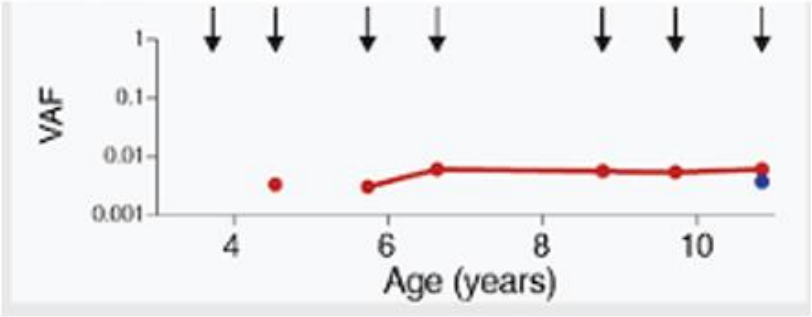
- Cytogenetics (chromosomes) and FISH: changes predictive of MDS/AML
  - monosomy 7
  - Complex (multiple) changes



- Deep sequencing for somatic mutations
  - Need to understand the patterns and their significance
    - Example: Shwachman Diamond Registry study

Clonal dynamics in SDS

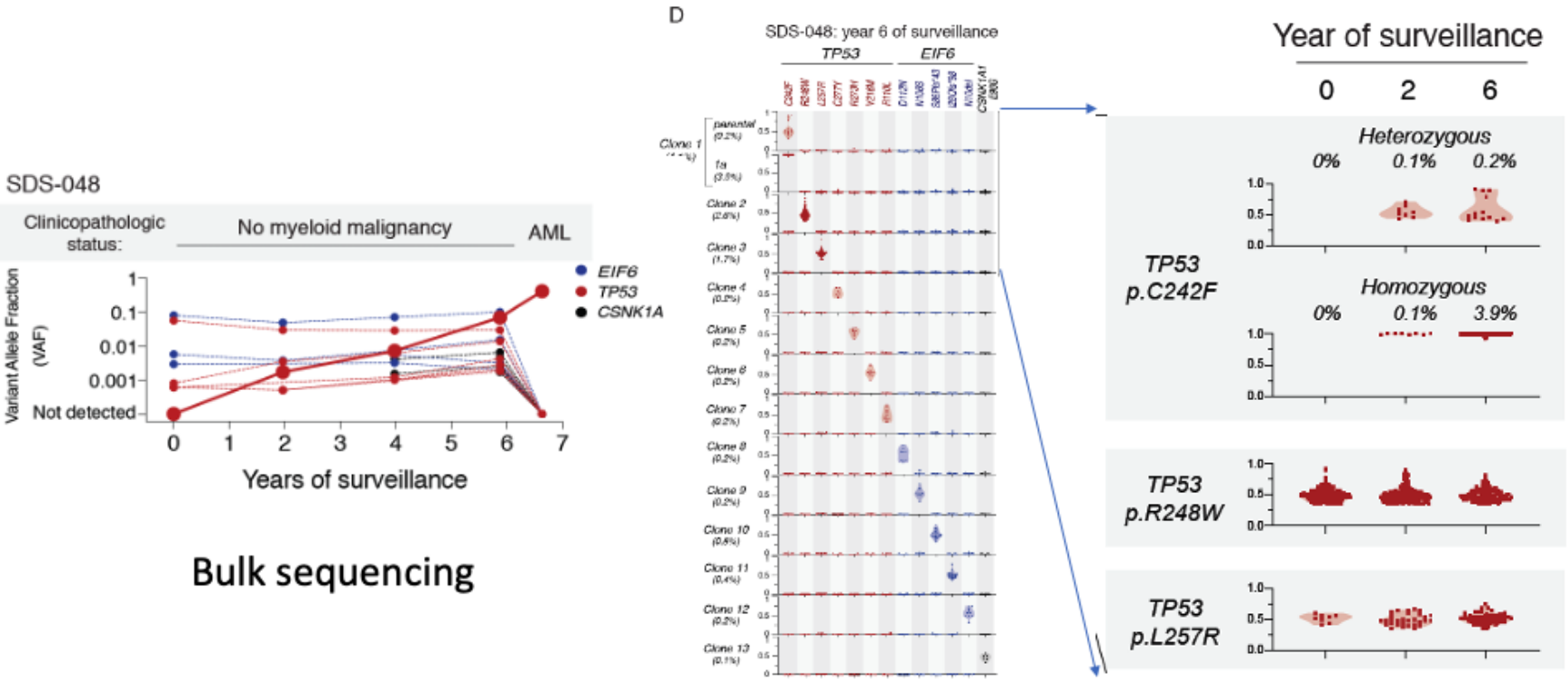




Nature Communications, 2021
Kennedy…Shimamura, Lindsley**

Shwachman Diamond Syndrome

Early identification of pre-leukemic subclones



Nature Communications, 2021 Kennedy…Shimamura, Lindsley**

Healthcare maintenance

- *"I don't need to see a doctor because I don't feel sick…"*
- The point is to partner with your hematologist to <u>keep you healthy.</u>
- Sometimes if you wait until you feel sick, the complications may be advanced and hard to treat
- Live your life!

Indications for Transplant

- MDS/AML
- MDS-associated cytogenetic abnormality
- Poor response to G-CSF
- Severely low blood counts or symptoms from low blood counts

Consider for:

- High dose of G-CSF required for ANC still <2000
- Intolerable side effects of G-CSF
- High risk features in bone marrow (including somatic mutation testing)

Probably not recommended:

- Doing well on low dose G-CSF
- Isolated small stable somatic mutations without additional concerning findings (clonal hematopoiesis)

Resources

- SCNIR
- SCN gene therapy pre-clinical sample donation: ***akiko.shimamura@childrens.harvard.edu***

- SDS Registry (url: SDSRegistry.org)
- SDS Board for physician consultation
  - Submit inquiry online through SDSRegistry.org, go to “Contact Us” page