Advances in treatment

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Changing Landscape of G-CSF: Biosimilars

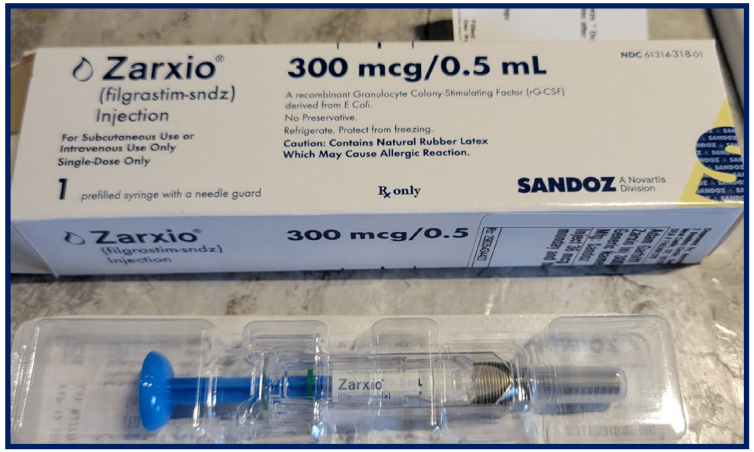
- Biosimilars offer options for G-CSF dosing
  - Neupogen®
  - Granix ®
  - Zarxio®
  - Nivestym ®
  - Releuko®
  - Zarxio®

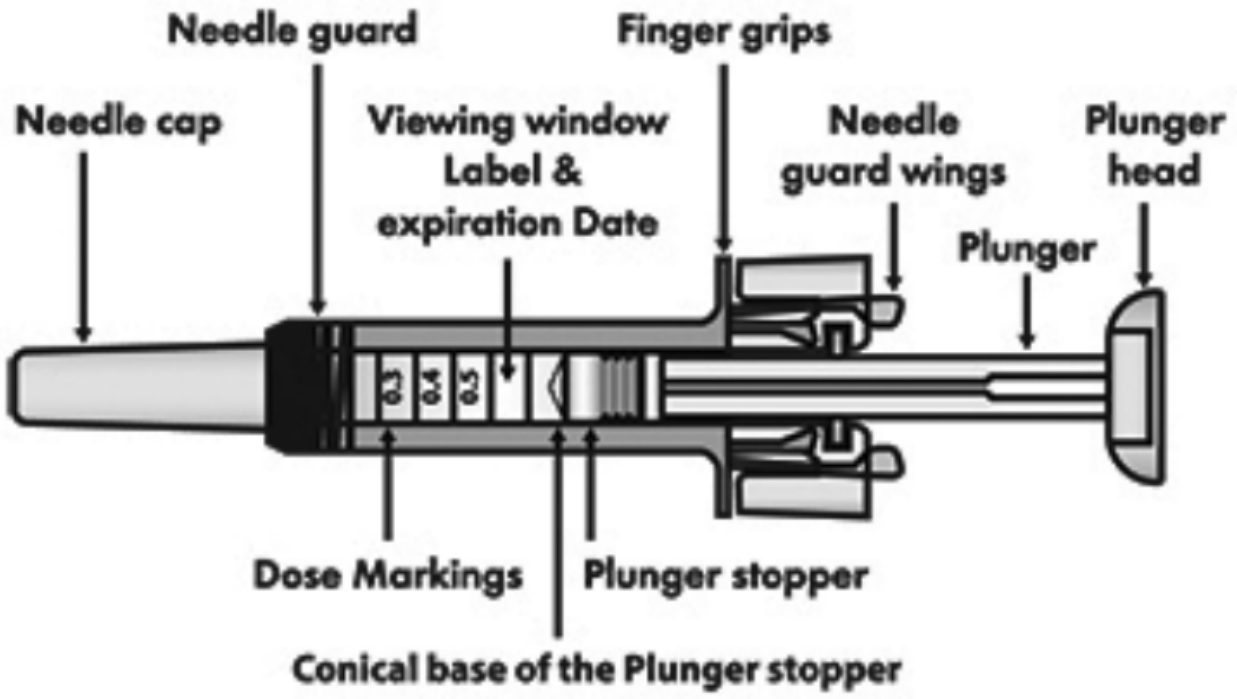
- No significant differences in reported adverse reactions
- Differences may exist in how the drug is supplied (pre-filled syringes, multi-use vials) and concentration

Filgrastim (G-CSF) biosimilars

- Dosage forms and strengths
  - Single dose vials: 300 mcg/1 mL or 480 mcg/1.6 mL
  - Prefilled syringes: 300 mcg/0.5 mL or 480 mcg/0.8 mL
  - Prefilled syringes are twice as concentrated
  - **Prefilled syringes cannot measure increments less than 0.1 mL (60 mcg)**
- **Prescribers are often not familiar with dosing limitations of pre-filled syringes**
- **Zarxio is only available in pre-filled syringes; cannot administer a dose less than 0.3 mL (180 mcg) in these syringes**

Picture Worth a Thousand Words





- A dose less than 0.3 mL cannot be accurately measured using the ZARXIO prefilled syringe.
- You should not inject a dose less than 0.3 mL (180 mcg) from a ZARXIO prefilled syringe.

Novel drugs - discussed by Dr. Dale

Advances in surveillance for MDS/AML in congenital neutropenia

- Current standard: bone marrow examination for cell content and chromosomal changes (e.g. monosomy [single copy] of Chr. 7)
- Somatic mutations: acquired genetic changes in bone marrow stem cells that may provide earlier prediction of MDS/AML
- Peripheral blood rather than bone marrow?? – maybe in the future

Advances in transplant

First, an overview

Slides adapted from presentations by my colleagues at Boston Children's Hospital

Overview

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment option, but candidates need to be appropriately selected as it is associated with 5-10% treatment related mortality and potential late effects

Indications for Allogeneic Transplant

Malignant Disease	Non-Malignant Disease		
Hematopoietic Malignancy	**Multi-lineage Disorders of Hematopoiesis**	**Metabolic Disorders**	**Lineage Specific Disorders**
<u>Leukemia</u> <u>AML/MDS</u> High risk or relapsed <u>ALL</u> Very high risk or relapsed <u>CML</u> Accelerated phase Blast crisis Poor response to TKI <u>Lymphoma</u> Refractory HL/NHL	• Aplastic anemia • Fanconi anemia • Other IBMFs	• Adrenoleukodystrophy • Mucopolysaccharidosis	<u>RBC</u> • Sickle cell disease • Thalassemia <u>Platelets</u> • CAMT • WAS <u>Neutrophils</u> • SCN • CGD • LAD <u>Lymphocytes</u> • SCID •Hyper IgM syndrome, WAS

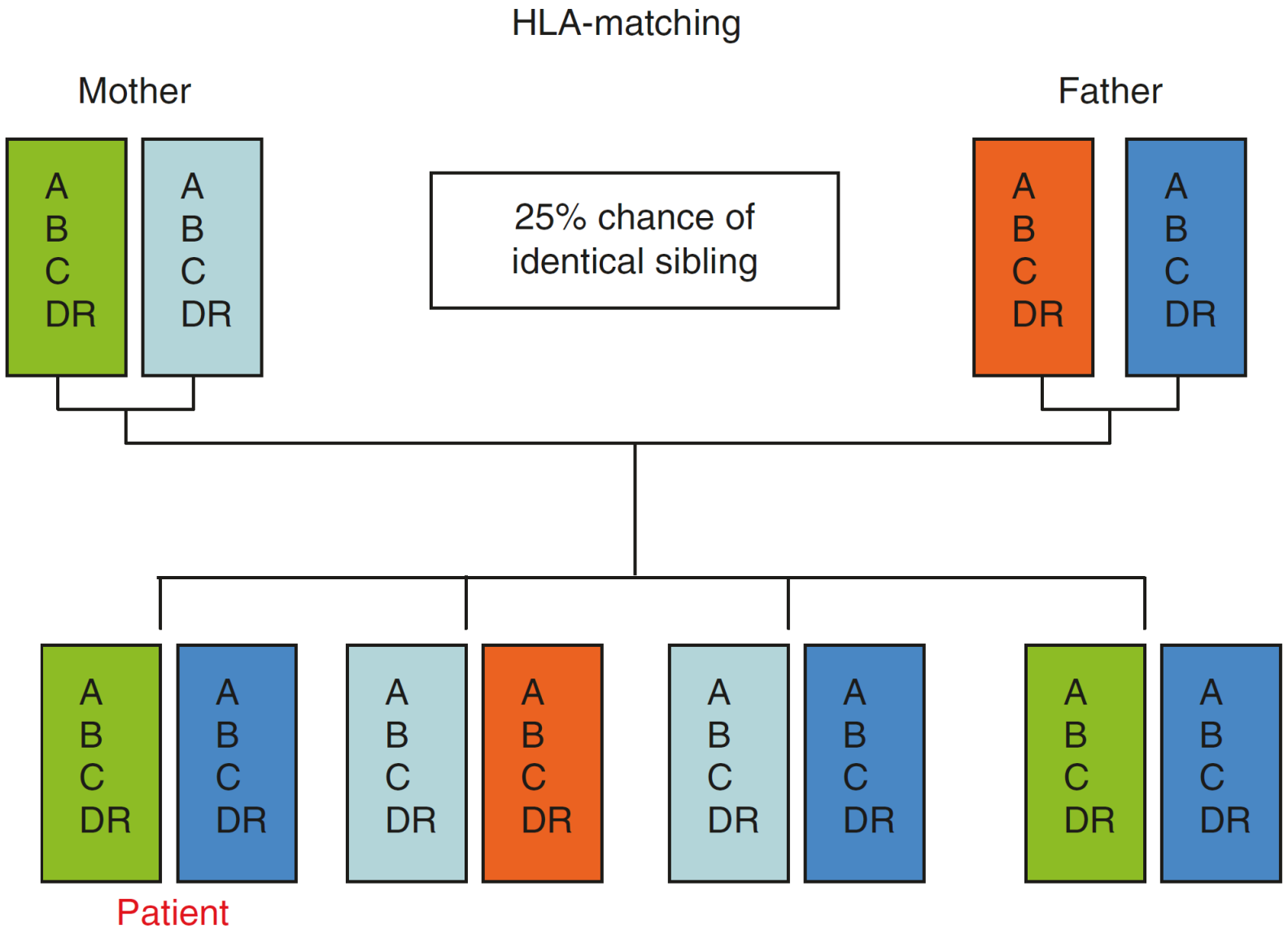
Types of transplant

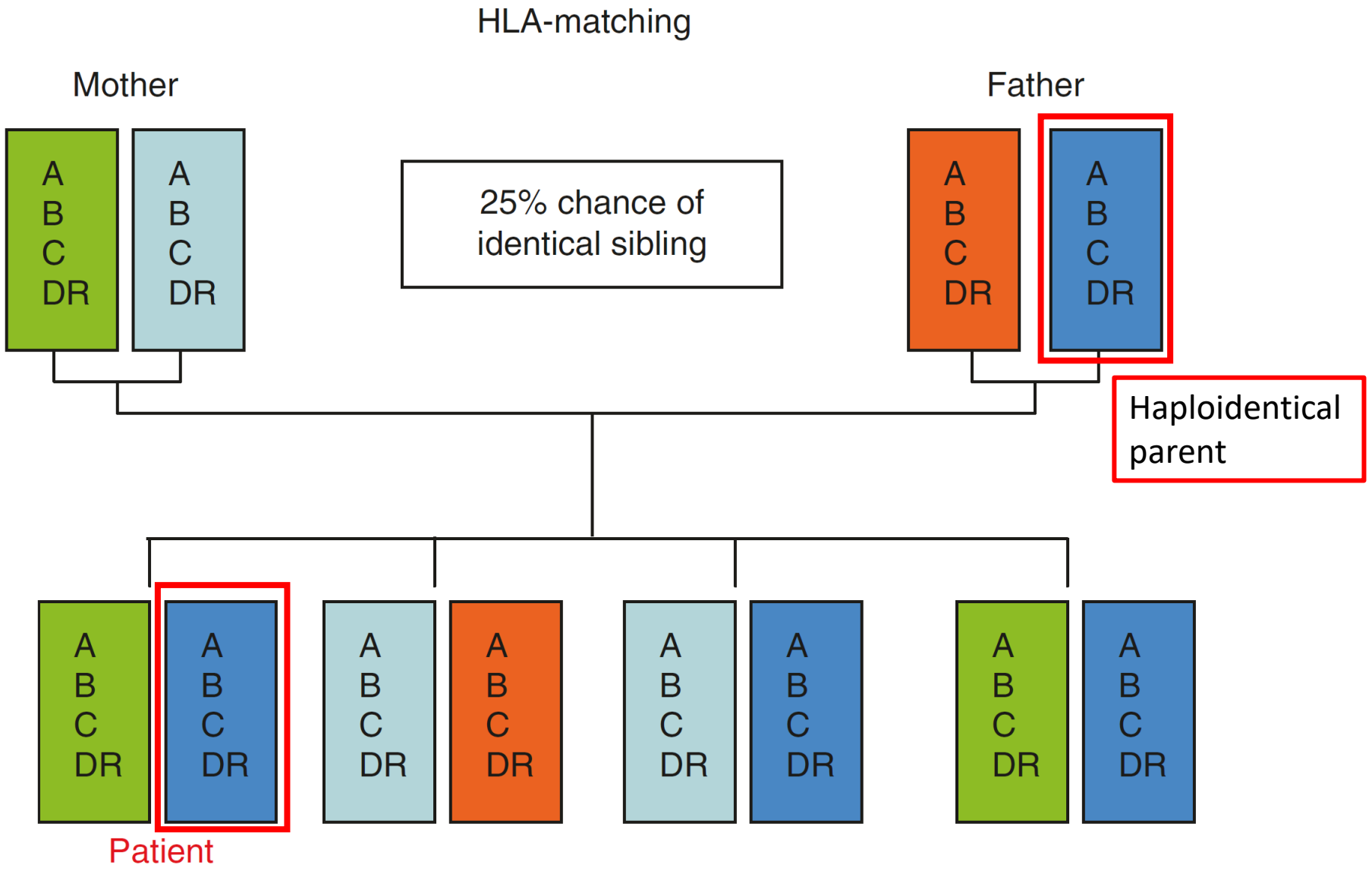
- Donor matching:
  - Autologous (self – e.g. gene therapy)
  - Matched related (usually a sibling)
  - Matched unrelated (~9 million donors in National Marrow Donor Program)
  - Mismatched unrelated – many different degrees of mismatch
  - Haplo-identical (half-matched, usually a parent)
- Sources of donor stem cells:
  - Bone marrow
  - Peripheral blood
  - Umbilical cord blood

HLA matching

- Identification of a matched donor is accomplished through “HLA typing” of family members and/or unrelated volunteers for a suitable match
  - A sibling has a 25% of being a ”full HLA-match” and 50% chance of being a “half HLA-match”, also called a haploidentical donor
  - A parent is almost always a “haplo” match and sometimes better

- The degree of HLA match and other donor factors such as age are important for reducing the risk of transplant


HLA-matching
Mother
Father
A
B
C
DR
25% chance of identical sibling
Patient


HLA-matching
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25% chance of identical sibling
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Haploidentical parent
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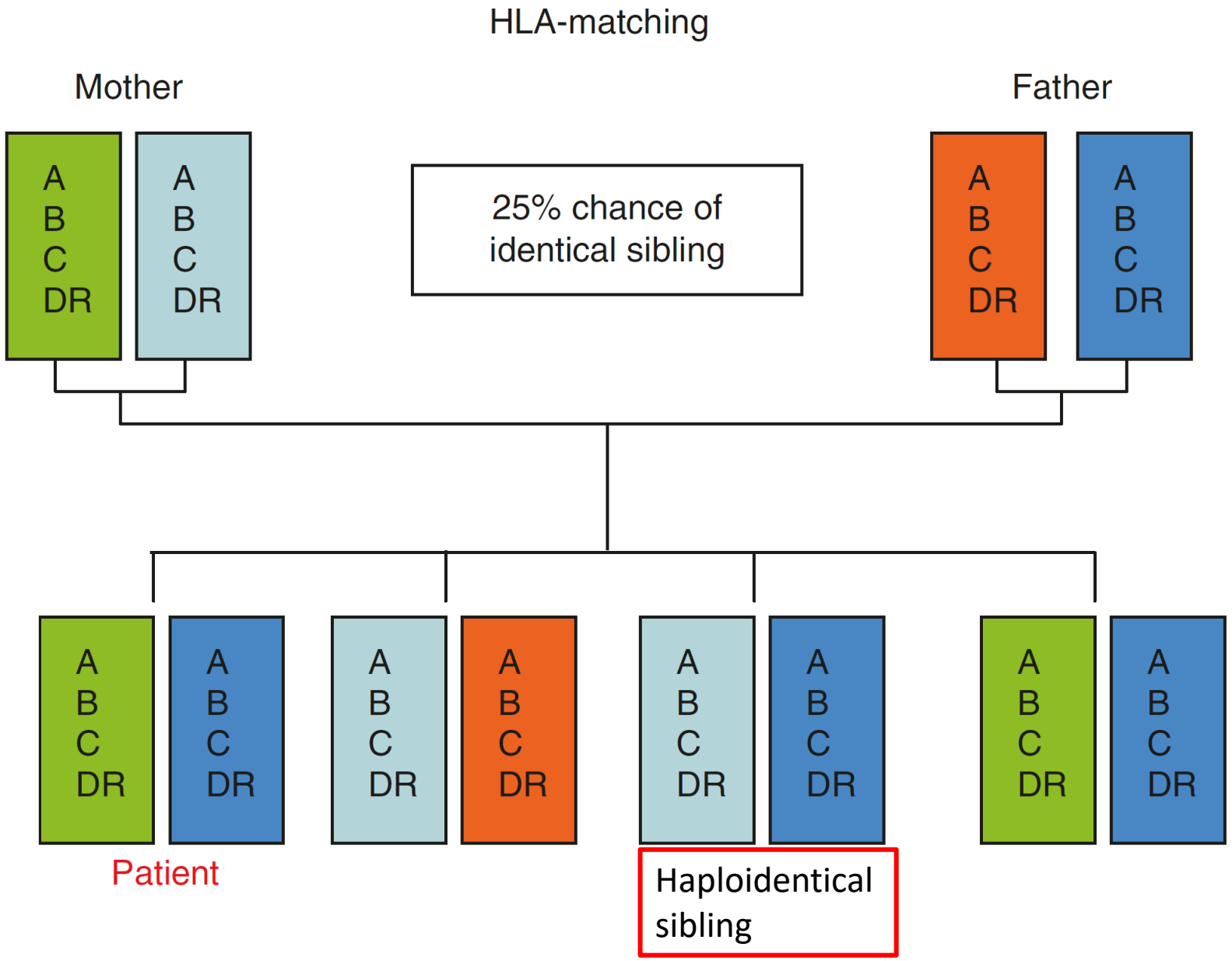
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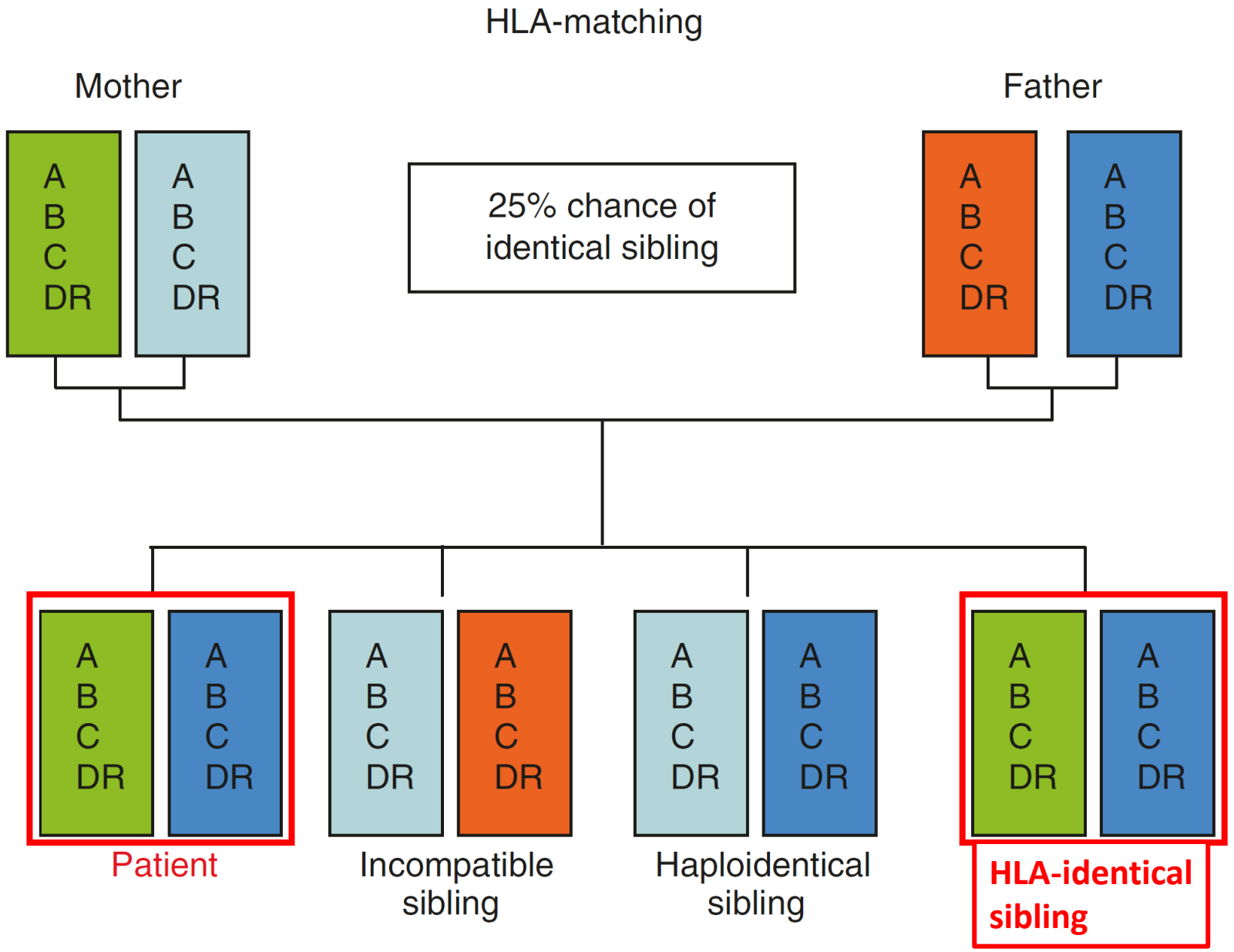
HLA-matching
Mother
Father
A
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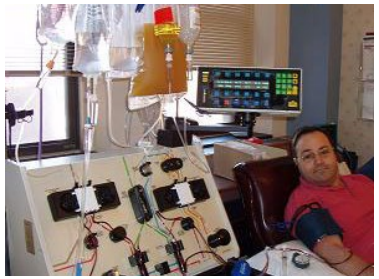
C
DR
25% chance of identical sibling
Patient
Incompatible sibling
Haploidentical sibling
HLA-identical sibling

Hematopoietic stem cell sources

Bone marrow



Peripheral blood

Umbilical cord blood

Advances in transplant

- Risks of death or severe complications are constantly improving
- Less toxic regimens are being developed
- New drugs for graft-versus-host disease (e.g. Abatacept)
- Nearly equal outcomes for related vs unrelated donors
- Amazingly good results with haplo-identical transplant – almost everyone has a possible donor
- Improved technologies for fertility preservation – male and female

Gene therapy

- Selective knockout – discussed by Emendo team
- Total knockout – in development by Boston and Tubingen (Germany) teams
  - Rationale: neutrophil elastase is dispensable
    - Papillon-Lefevre syndrome, a loss of four neutrophil protease enzymes including elastase, is quite mild
  - Efficiency is high and the same reagents can be applied to all patients with *ELANE* neutropenia
  - Base editing approaches in development will not involve DNA cuts that can produce genetic damage

Gene therapy

Downside: still requires autologous transplantation of stem cells

- Bone marrow or peripheral blood stem cell harvest
- Conditioning as for transplant
- Period of very low blood counts and immune deficiency
- NO risk of GVHD

Questions…

If you dare