# ICD-10-CM Code Request for
# **Shwachman-Diamond Syndrome**

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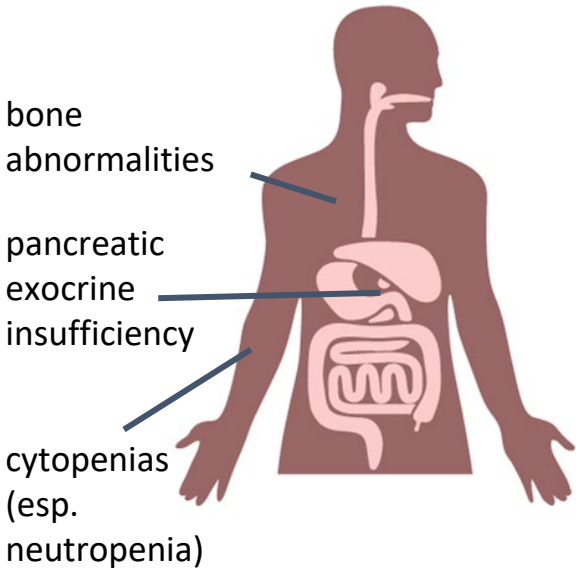
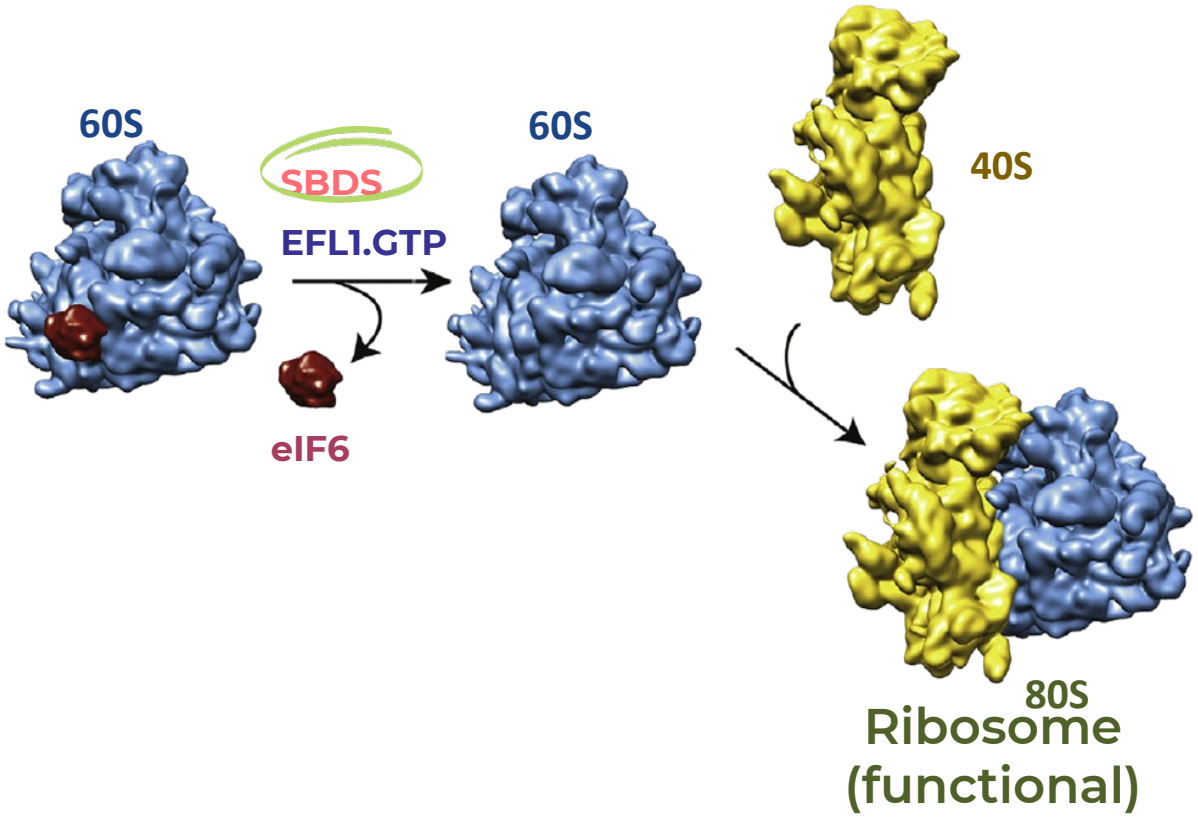
SHWACHMAN-DIAMOND SYNDROME ALLIANCE

# Shwachman-Diamond Syndrome (SDS)

- Inherited bone marrow failure syndrome characterized by the clinical triad of pancreatic insufficiency, cytopenias (esp. neutropenia) and bone abnormalities first described in 1964.
- Diagnosis relies on:
  - exocrine pancreatic insufficiency and bone marrow failure and/or
  - identification of biallelic pathogenic variants in *SBDS*, *EFL1*, or *DNAJC21*, or a heterozygous pathogenic variant in *SRP54* by molecular genetic testing.
- 90% of cases attributed to biallelic pathogenic variants in SBDS; 10% have no known genetic cause and may have a different natural history.
- All the genes associated with SDS are involved in the ubiquitous pathway of ribosome biogenesis (assembly) and function.



# Molecular Biology of the SBDS Protein




- SBDS assists in the removal of eIF6 from the 60S ribosomal subunit to allow the 60S and 40S subunits of ribosome to join and form the transcriptionally active 80S ribosome.
- In SDS, there is not enough SBDS protein — therefore not enough working ribosomes — causing ribosomal stress.
- SBDS may be involved in additional cellular functions, such as cell division.

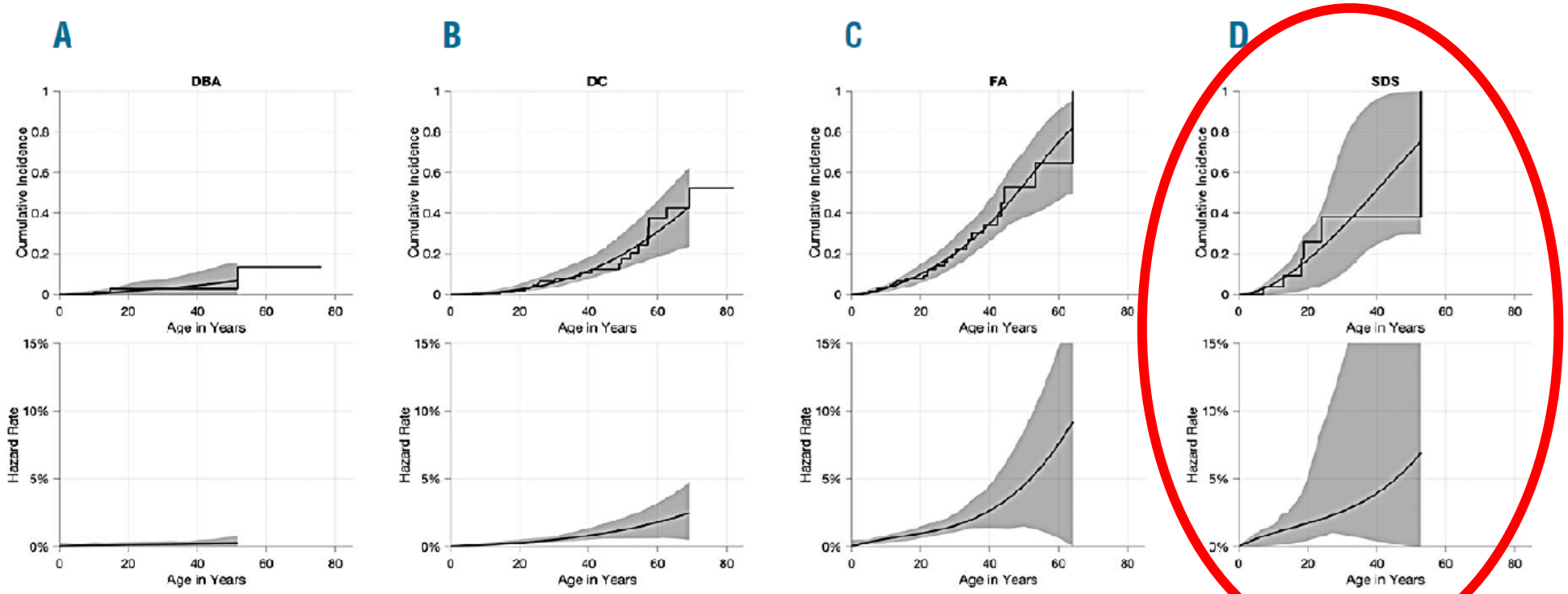
A.J. Warren / Advances in Biological Regulation 67 (2018) 109e127

# Complications & Incidence of SDS

- SDS patients are at high risk of developing life-threatening hematological complications, such as severe bone marrow failure, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), which are estimated to occur in over 30% of patients with biallelic SBDS mutations by age 30[1].
- ***The estimated incidence of SDS is 1:76,000[2], but is likely severely underdiagnosed.***
- It is anticipated that substantially more individuals will be identified as genetic and biochemical testing becomes more widely adopted. For example, in a cohort of early MDS/AML patients (age <40 years), genetic screening identified 4% of patients to have SDS[3].

[1]Donadieu J et al. Haematologica. 2012;97:1312–9
[2]Goobie S et al. Am J Hum Genet. 2001 Apr;68(4):1048-54.
[3]Lindsley RC et al. N Engl J Med. 2017, Feb 9;376(6):536-547.

# Cumulative Incidence/Hazard Rate MDS in BMF

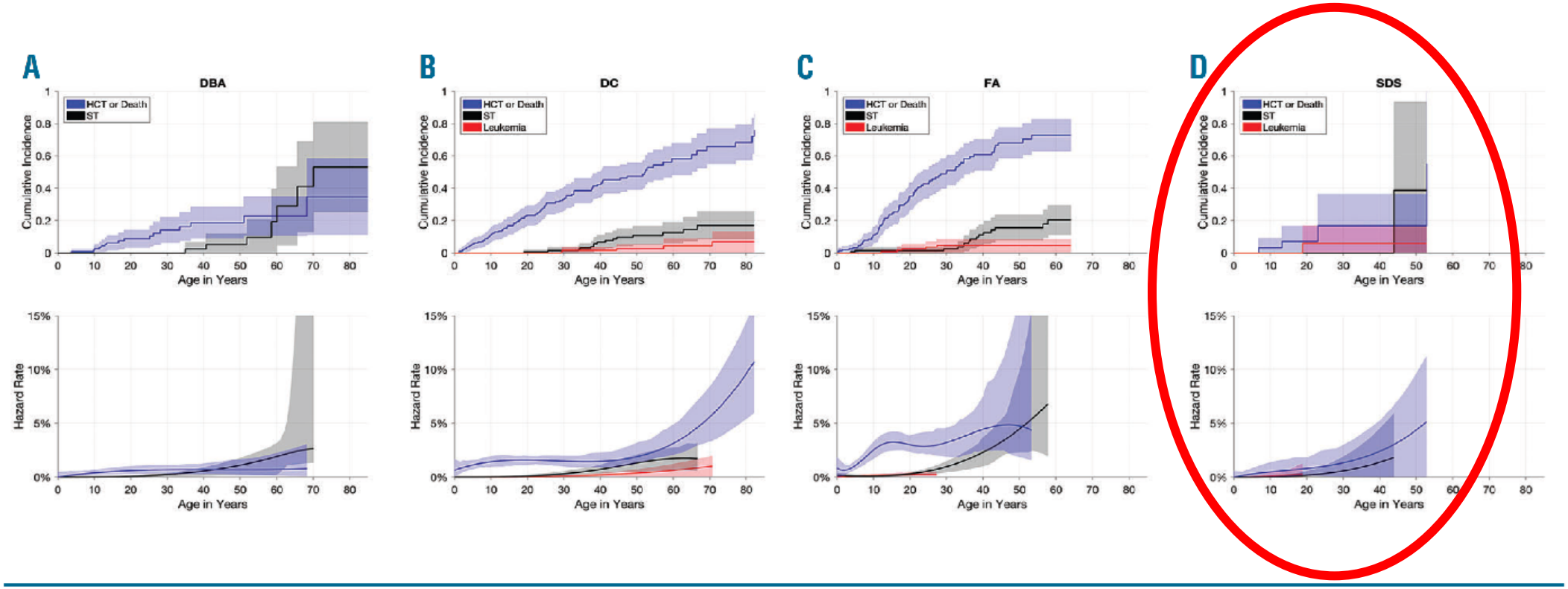



**Steep increase of cumulative incidence and annual hazard ratios of MDS by age in SDS patients, in comparison with other bone marrow failure disorders (BMFs).**

**Figure 2. Cumulative incidence and annual hazard rates of myelodysplastic syndrome (MDS) by age.** Patients with (A) Diamond-Blackfan anemia (DBA), (B) Dyskeratosis congenita (DC), (C) Fanconi anemia (FA) and (D) Shwachman-Diamond syndrome (SDS). Top panels show observed (stair-step lines) and modeled (smooth curves) cumulative incidence curves. Bottom panels show hazard rates (smooth curves) as described in Figure 1. MDS is not considered a competing risk.

Alter BP et al. Hematologica 2018 Jan;103(1):30-39.

# Cumulative Incidence/Hazard Ratios for Malignancy, HSCT and Death in BMF

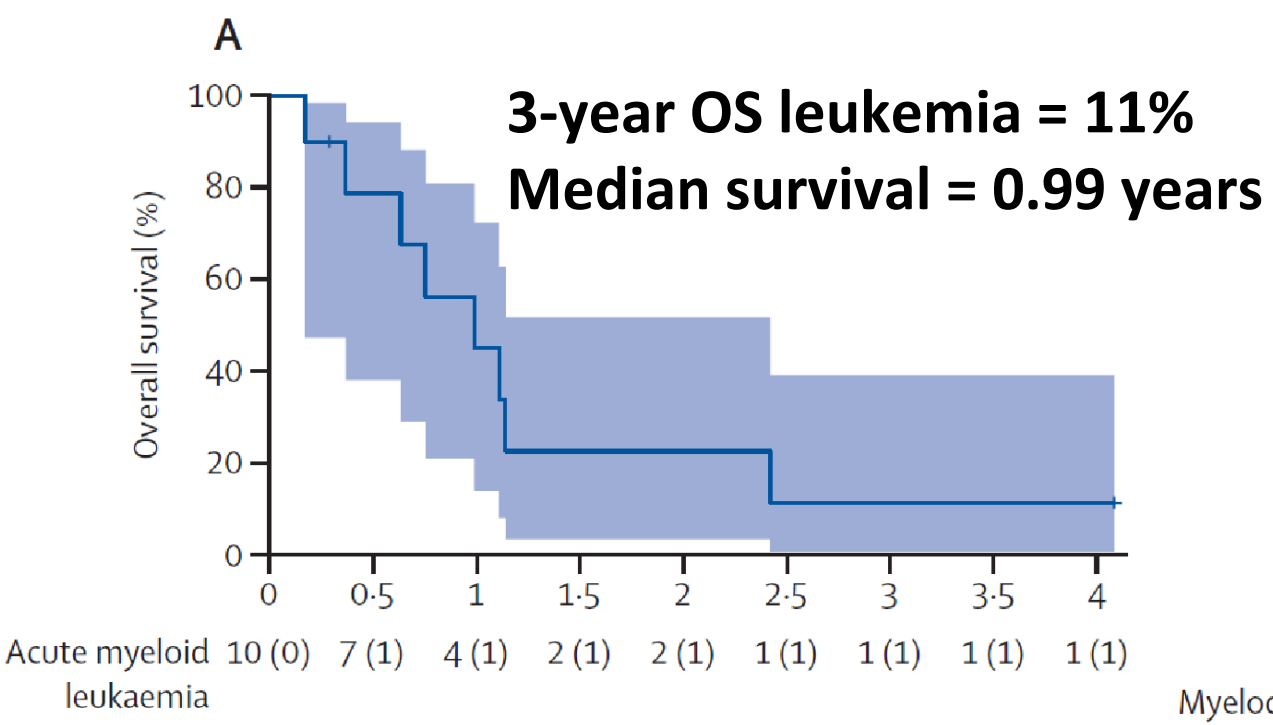


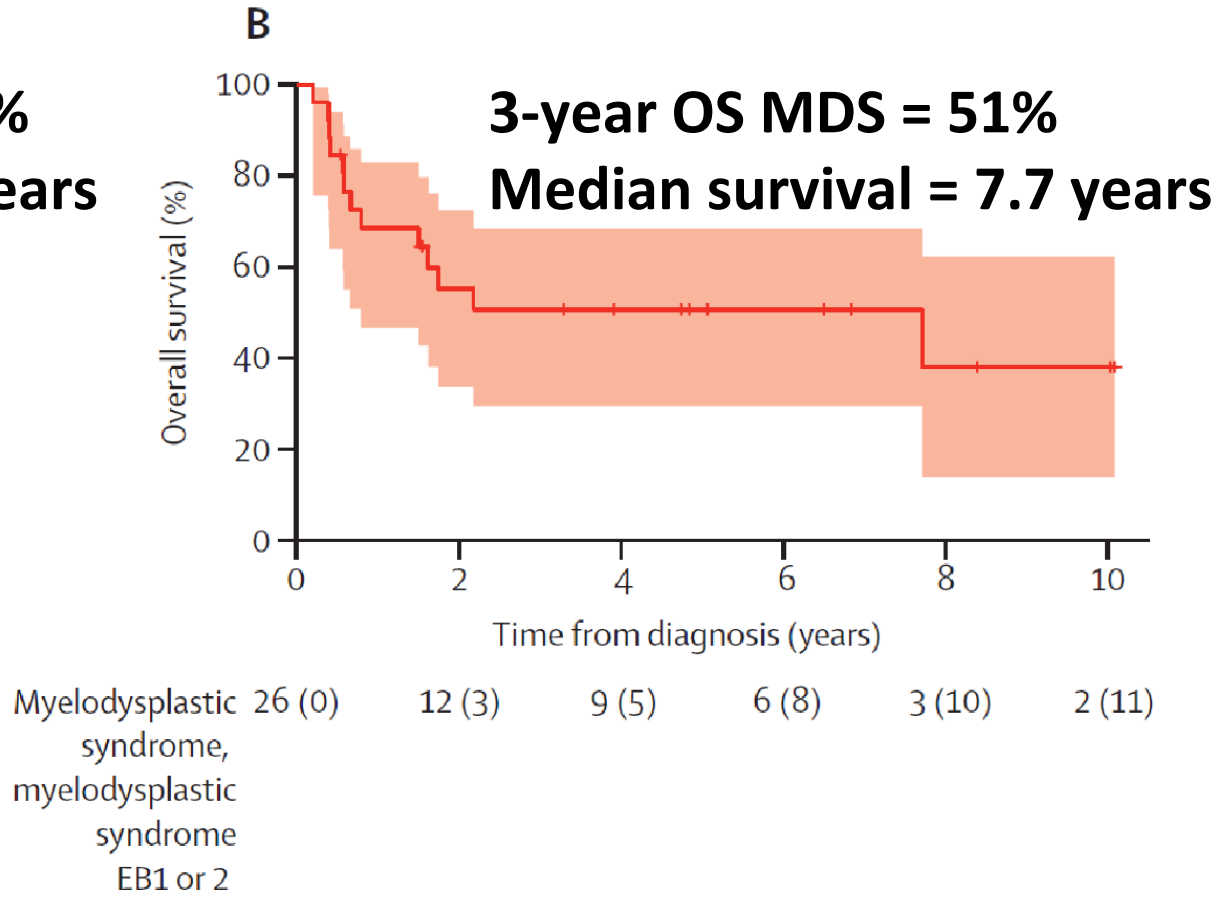

**Steep increase of cumulative incidence and annual hazard rates of hematopoietic cell transplantation or death (HCT or Death), acute leukemia, or solid tumors (ST), by age in SDS patients, in comparison with other bone marrow failure disorders (BMFs).**

**Figure 1. Complications in patients in the NCI inherited bone marrow failure syndromes cohort.** (A-D) Cumulative incidence (top panels) and annual hazard rates (bottom panels) of competing adverse events by age in patients with (A) Diamond-Blackfan anemia (DBA), (B) Dyskeratosis congenita (DC), (C) Fanconi anemia (FA) and (D) Shwachman-Diamond syndrome (SDS). Adverse events are severe bone marrow failure leading to hematopoietic cell transplantation or death (HCT or death, blue), acute leukemia (red), or solid tumors (ST, black). Top panels, cumulative incidence of experiencing each event as the initial cause of failure (observed, stair-step lines) and 95% confidence intervals (shaded areas). Bottom panels, annual hazard rates (modeled, smooth curves), i.e., % per year who develop a given event type among subjects who are still susceptible, and 95% confidence intervals (shaded areas).

Alter BP et al. Hematologica 2018 Jan;103(1):30-39.

# Malignancy Outcomes in SDS are Dismal




Myers K et al. Lancet Haematol. 2020 Mar;7(3):e238-e246.

# HSCT Outcomes in Congenital Neutropenia

| Post-HSCT Overall Survival | Without malignancy | With Malignancy |
|---|---|---|
| SCN | | |
| * EBMT[38] | 87% (n=73) | 79% (n=14) |
| * SCNIR (European)[39] | 78% (n=27) | 83% (n=24) |
| SDS | | |
| ^ CIBMTR[41] | 72% (n=39) | 15% (n=13) |
| ^ SAAWP-EBMT[40] | 71% (n=61) | 29% (n=13) |
| * SDSR[42] | ----- | 46% (n=15) |

*3-year overall survival

^5-year overall survival

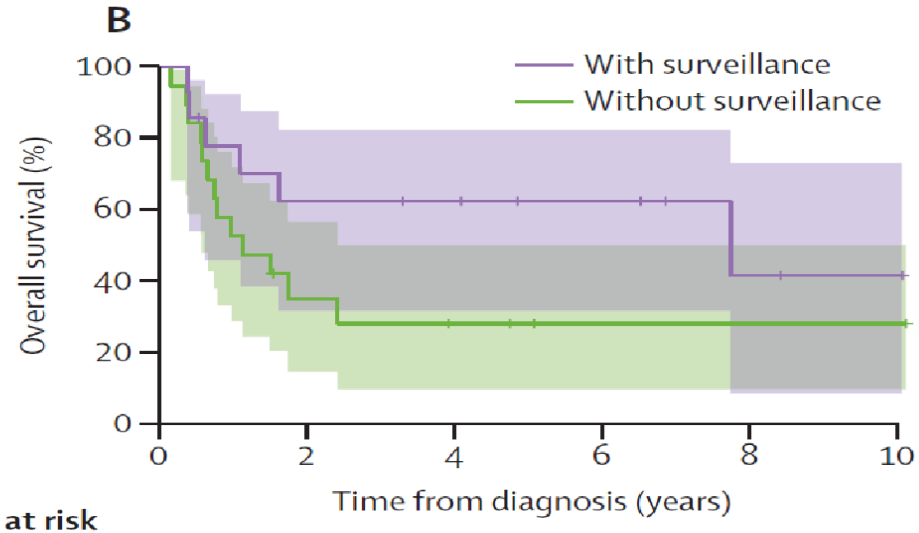
Warren J and Link DC. ASH Educ. 2021 Dec 10;2021(1):514-520.

# Impact of Surveillance for SDS

**Table 1**
**Clinical evaluation for patients with Shwachman-Diamond Syndrome**

| | Frequency |
|---|---|
| Hematology | |
| CBC | Diagnosis, every 3–6 mo or as indicated |
| Bone marrow aspirate and biopsy | Diagnosis, every 1–3 y or as indicated |
| Iron, folate, $B_{12}$ | Diagnosis, as clinically indicated |
| Immunoglobulins and lymphocyte subpopulations | Diagnosis, as clinically indicated |
| HLA testing | As clinically indicated, impending BMT |
| Gastroenterology | |
| Pancreatic enzyme measurement | Diagnosis, as clinically indicated |
| Fat-soluble vitamins and prothrombin time | Diagnosis, 1 mo after commencement of enzyme therapy, then 6–12 mo as indicated |
| Hepatic profile | Diagnosis, yearly or as clinically indicated |
| Pancreatic imaging | Diagnosis |
| Endoscopy | As clinically indicated |
| Skeletal system | |
| Growth evaluation: Height, weight, head circumference | Yearly (more frequently if on GH replacement) |
| Skeletal survey | Diagnosis, as clinically indicated |
| Bone densitometry | Adulthood, as clinically indicated |
| Other evaluations | |
| Neuropsychological testing | Diagnosis, regular assessment during school years 6–8, 11–13, 15–17 y |
| Endocrine evaluation (eg, TSH, GH) | As clinically indicated |
| Auditory testing | As clinically indicated |

*Abbreviations:* BMT, bone marrow transplantation; CBC, complete blood count; GH, growth hormone; TSH, thyroid-stimulating hormone.




| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| Without surveillance | 19 (0) | 5 (2) | 3 (3) | 1 (5) | 1 (5) | 1 (5) |
| With surveillance | 14 (0) | 8 (1) | 7 (2) | 5 (4) | 2 (6) | 1 (7) |

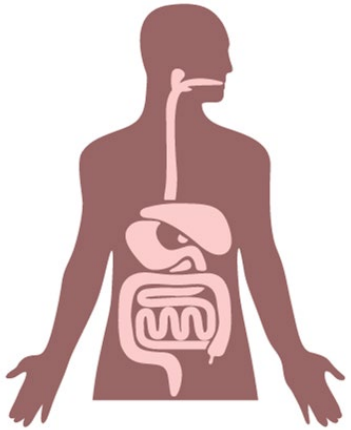
3-year OS for SDS patients with MDS/AML: 28% without surveillance and 62% with surveillance

Myers K et al. Lancet Haematol. 2020 Mar;7(3):e238-e246.

Nelson AS and Myers K. Hematol Oncol Clin North Am 2018 Aug;32(4):687-700.

# ICD-10 Codes Currently Used for SDS symptoms

Codes cover various symptoms or complications associated with SDS but are not specific for SDS or useful to identify SDS patients to aid in proper management and research.



**Blood and Immune System**

- D70.9 Neutropenia, unspecified
- D64.9 Anemia, unspecified
- D69.6 Thrombocytopenia, unspecified
- D80 Immunodeficiency with predominantly antibody defects

**Infection**

- A41 Sepsis
- Chronic ear infections

**Musculoskeletal System**

- P94.9 Disorder of muscle tone of newborn, unspecified
- Q76.6 Other congenital malformations of ribs
- R62.52 Short stature (child)

**Failure to thrive**

P92.6 Failure to thrive in newborn
R62.51 Failure to thrive (child)

**Hematological Malignancies**

- C92.- Acute myeloblastic leukemia (AML)
- D46.- Myelodysplastic Syndromes

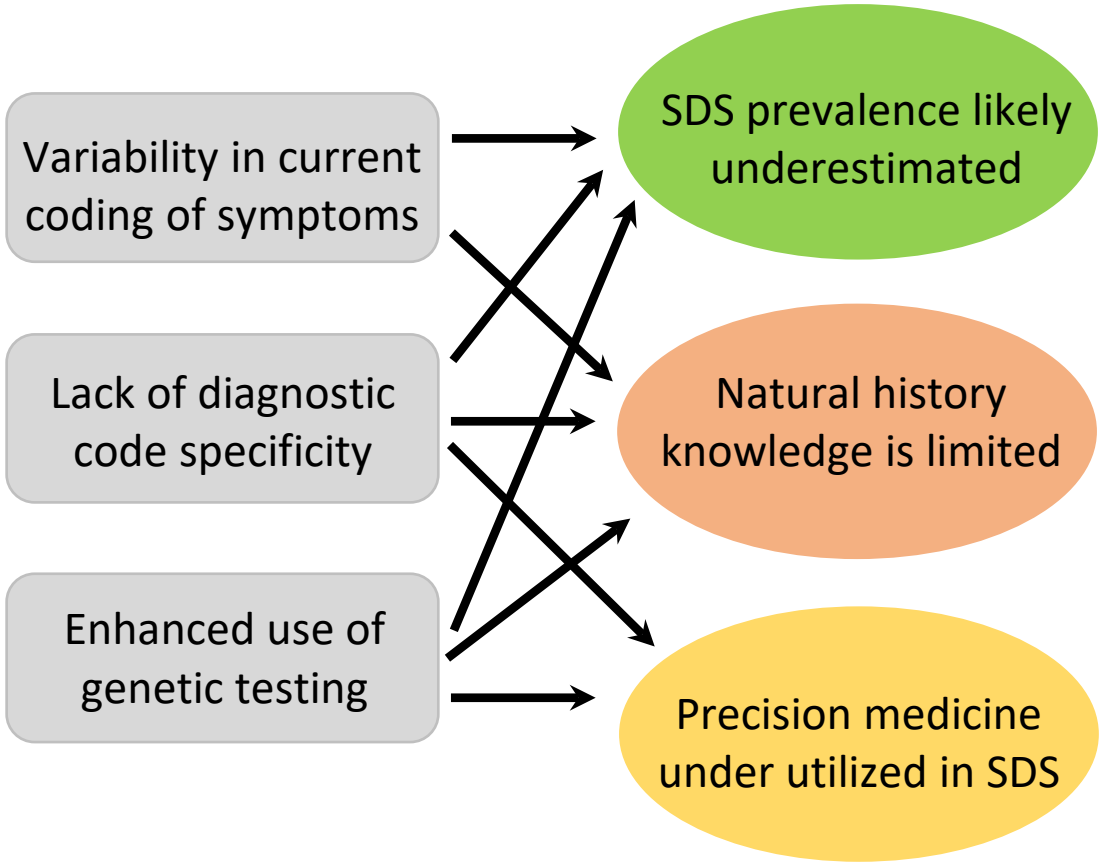
**Gastroenterology**

- K90.3 Pancreatic steatorrhea
- R19.5 Other fecal abnormalities
- R74.01 Elevation of levels of liver transaminase levels

**Neurodevelopmental**

- F80.9 Developmental disorder of speech and language, unspecified
- F84.0 Autistic disorder
- R62.0 Delayed milestone in childhood
- R62.5 Other and unspecified lack of expected normal physiological development in childhood

# Rationale for a New ICD-10-CM Code for SDS




- Enable more **accurate quantification of the prevalence** of SDS
- Facilitate **better definition of the natural history** of both known (esp. malignant) and emerging (e.g. immunodeficiency and inflammatory) phenotypes of SDS to provide better anticipatory guidance/monitoring for complications
- **Promote identification** of SDS patients most likely to benefit from targeted therapeutics and/or modifications of classical therapy