Genomics in MPN

Beyond *JAK2* / *CALR* / *MPL*

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Outline

- What is NGS
- Why is it necessary
- Challenges in 2025
- Future directions

Next generation sequencing

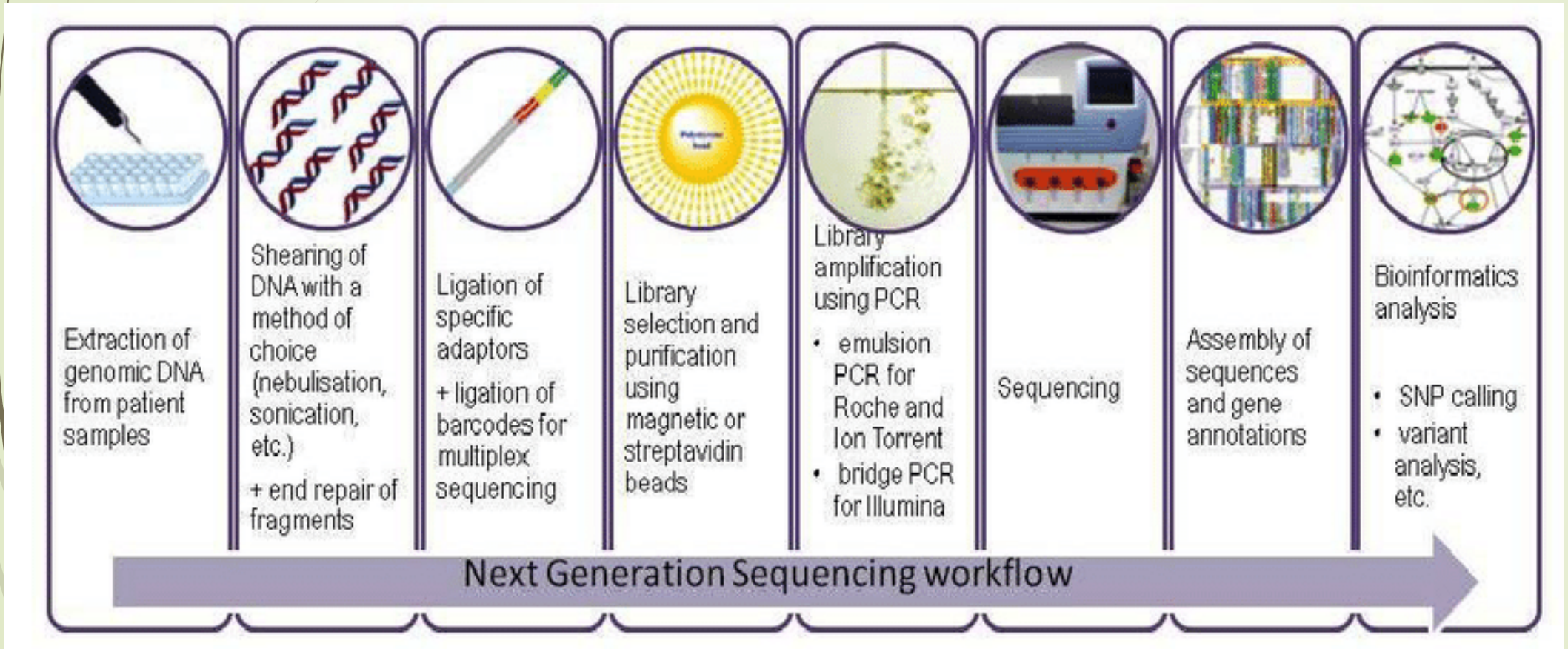


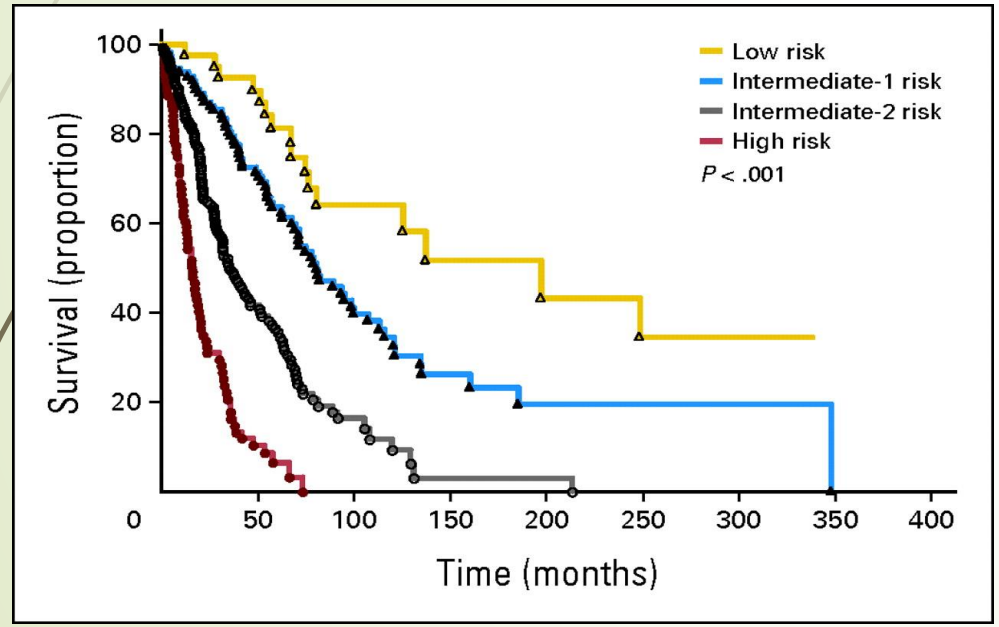
Image from *Petric et al. Next generation sequencing applications for breast cancer research. Clujul medical. 2015 Jul 1;88(3):278.*

Role of NGS in MPN panel

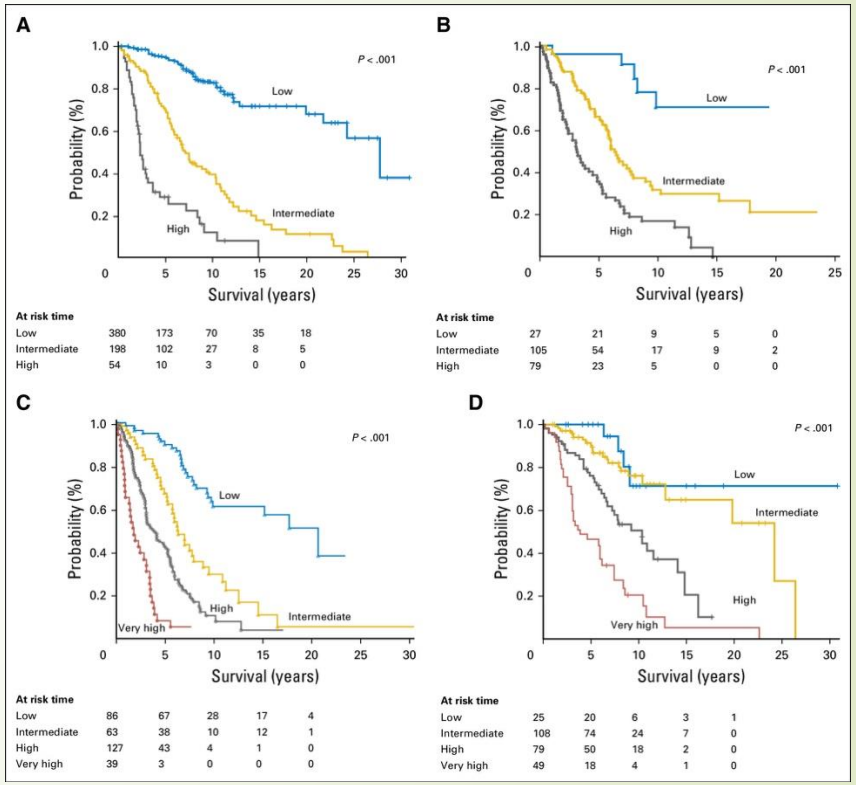
- Diagnostic
  - "One-stop shop" – covers the *JAK2* / *CALR* / *MPL* genes in one assay
  - Clonal marker for triple-negative MPN
  - Other differential diagnoses
    - Overlap syndromes (MDS/MPN) – *CSF3R; SF3B1* / *TET2-SRSF2* combination
- Prognostic
  - ~80% PMF patients harbour other myeloid mutations (*ASXL1* / *TET2* / *SRSF2* / *U2AF1*)
- ?Therapeutic

Prognostication in PMF

- Primary myelofibrosis
  - "Classical" prognostic systems: IPSS, DIPSS, DIPSS+
    - Age, Hb, WCC, constitutional symptoms circulating blasts%
    - "+" – platelet count, transfusion dependence, karyotype



Gangat et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. Journal of clinical oncology. 2011 Feb 1;29(4):392-7.

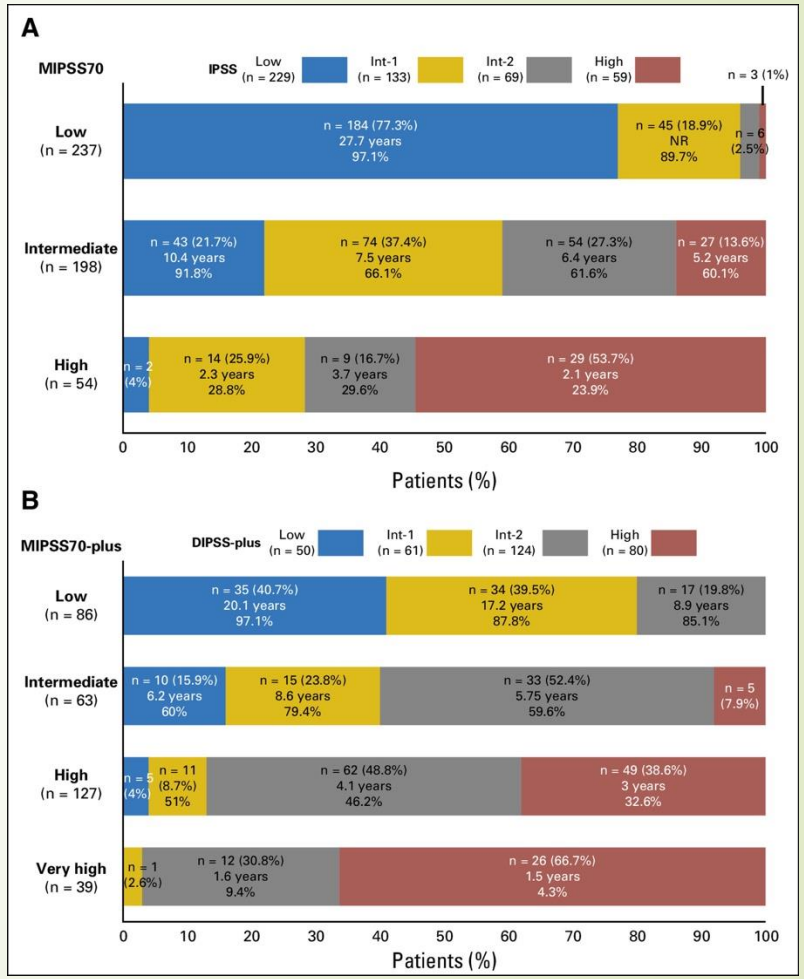


Guglielmelli et al. MIPSS70: mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. Journal of Clinical Oncology. 2018 Feb 1;36(4):310-8.

Prognostication in PMF

- MIPSS70 & MIPSS70+
  - Absence of Type 1-like CALR mutation
  - HMR mutations - *ASXL1 / EZH2 / SRSF2 / IDH1/2*
  - ≥ 2 HMR mutations
- MIPSS70+ v2.0
  - Addition of *U2AF1 Q157* as high risk

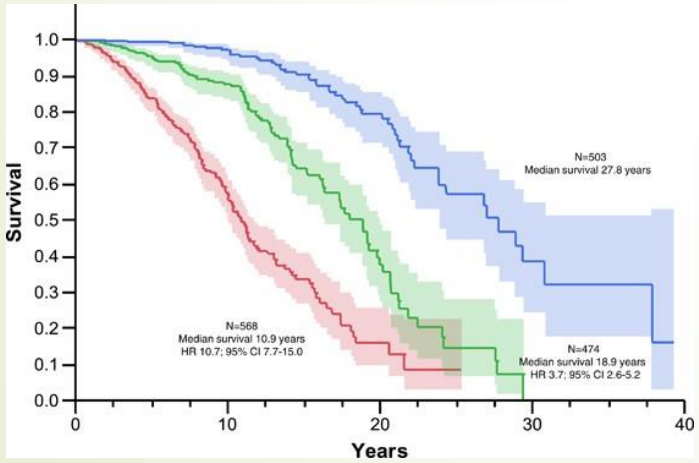
- MIPSS70+ v2.0 developed with selection of patients for allograft (median OS predicted to be less than 5 years) but subsequently shown to be prognostic in older patients
- IPSS / DIPSS / DIPSS+ still used for PBS access to ruxolitinib



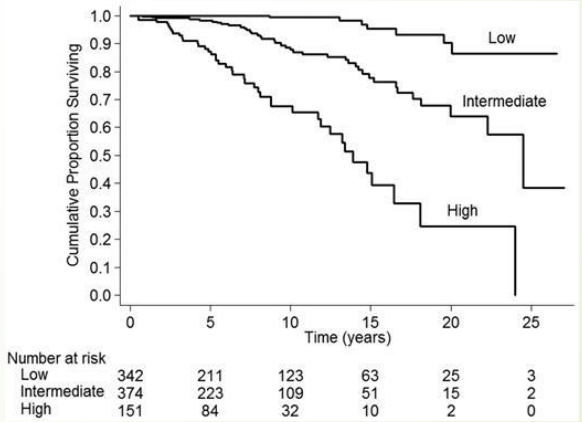
Guglielmelli et al. MIPSS70: mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. Journal of Clinical Oncology. 2018 Feb 1;36(4):310-8.

Prognostication in PV and ET

- Age is the strongest determinant of survival
- IWG (PV)
  - age ⩾67 years (5 points), age 57–66 years (2 points), leukocyte count ⩾15 × 10^9/l (1 point) and venous thrombosis (1 point), to devise a prognostic model that included low-risk (0 points), intermediate-risk (one or 2 points) and high-risk (⩾3 points) categories.
- IPSET (ET)
  - age ≥ 60 years (2 points), leukocyte count ≥ 11 × 10^9/L (1 point), and history of thrombosis (1 point)



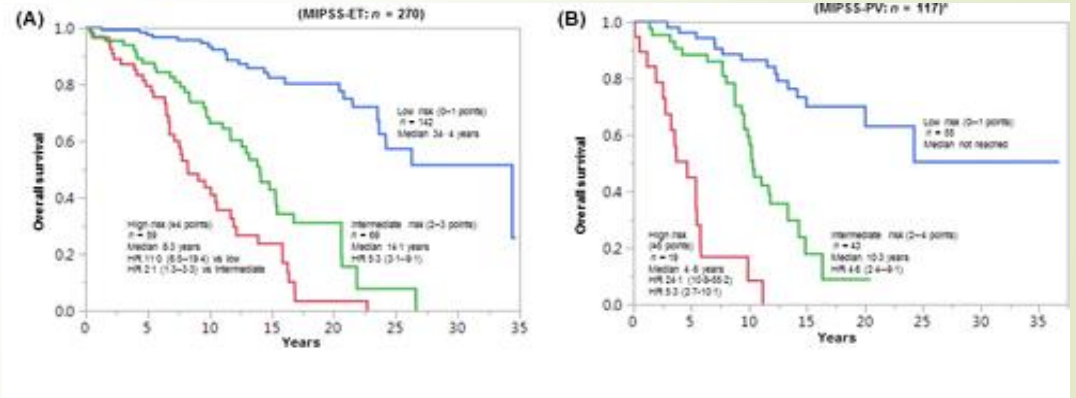
Tefferi et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera Leukemia. 2013 Sep;27(9):1874-81.



Passamonti et al. A prognostic model to predict survival in 867 World Health Organization–defined essential thrombocythemia at diagnosis, Blood, 2012 Aug 9;120(6):1197-201.

MIPSS-PV and MIPSS-ET

- More challenging due to lower frequencies of adverse mutations
- Predictors of adverse OS: *SRSF2* (PV); *SRSF2* and *SF3B1* (ET)
- Myelofibrosis-free survival: *U2AF1* and *SF3B1* in ET
- *TP53* predicted blast transformation in ET
- Adverse mutations (*SRSF2* / *SF3B1* / *U2AF1* / *TP53* in ET; *SRSF2* in PV) – 10% in ET and 2% in PV
- HR 2.4 in ET
- HR 7.8 (CI 3-17) in PV



Tefferi et al. Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera. British journal of haematology. 2020 Apr;189(2):291-302.

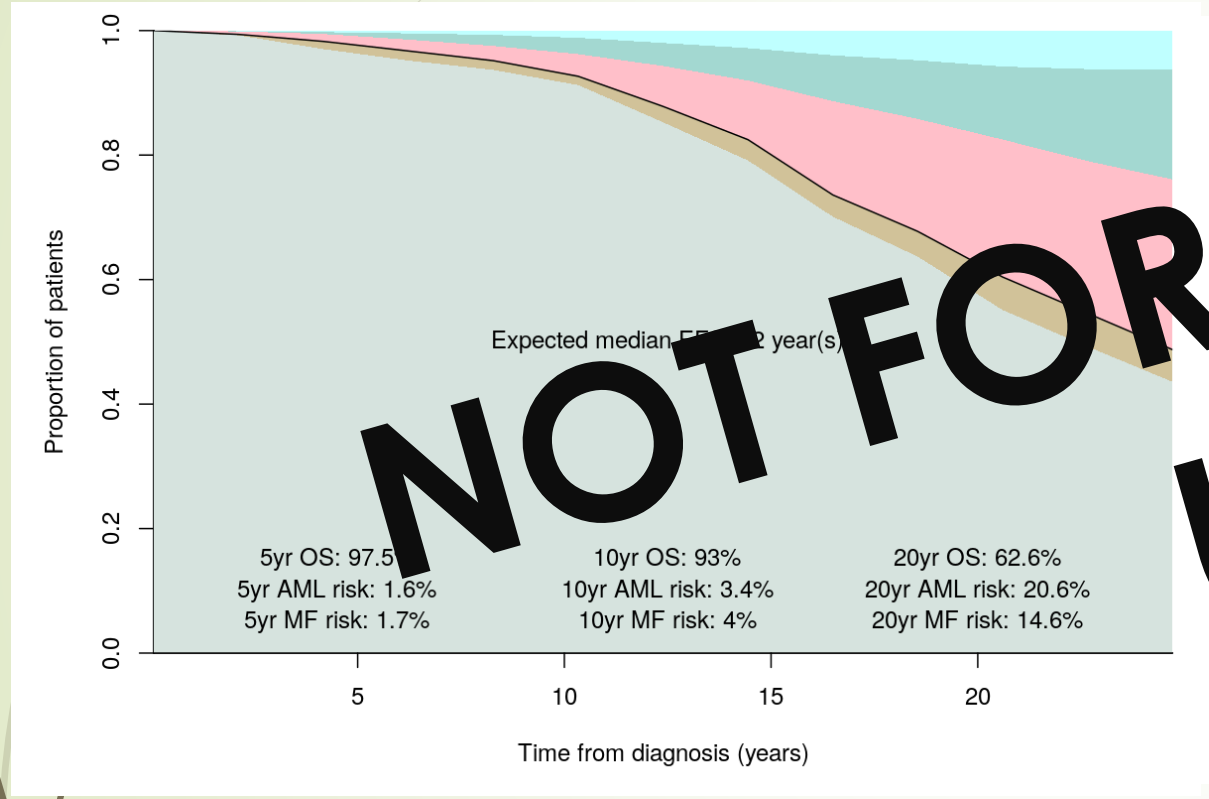
Reasons not to pursue additional testing

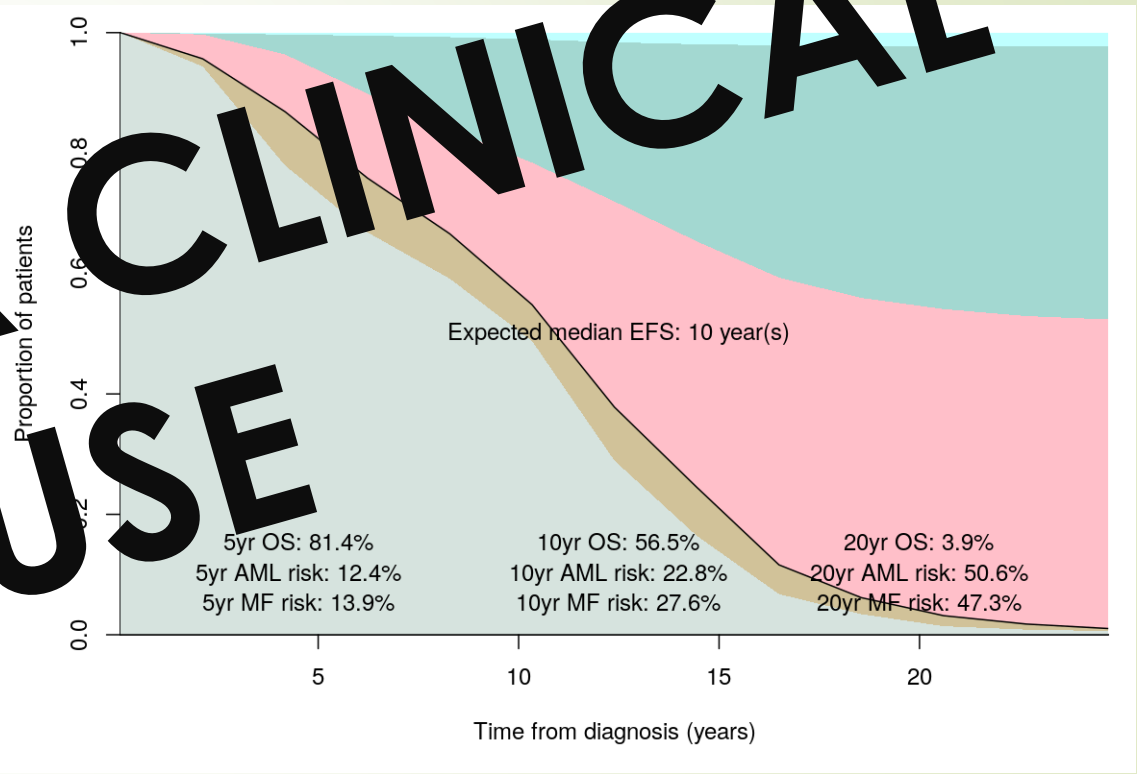
- (Cost)
- Provoke anxiety without interventions available to alter the natural history
- Incidental findings
  - Potential germline variants requiring follow-up testing
    - Patient cost
    - Healthcare costs

Challenges

- 50 yo man
- Incidental diagnosis - Hb 220 when presented for routine venesection for homozygous C282Y
- JAK2 exon 12 mutation; Dx Sept 2023
- NGS: *SRSF2* VAF 39%; *IDH1* 26%; *IDH2* x 2 variants R140W and R140Q 5% and 4% each
- MIPSS-PV – 3 points for adverse risk due to *SRSF2* mutation; median OS 13 years

Progress





NOT FOR CLINICAL USE

https://www.sanger.ac.uk/tool/progmod/progmod/

Future directions

- Molecular-targeted therapy
  - CALR monoclonal antibodies and Bi-specific T-cell engagers
  - Combination therapies – Ruxolitinib + MDM2 inhibitor
- Predictive models
  - Machine-learning
- Pandora's box
  - Germline variants carrying increase risk of MPN