ERIC study on prognostic and predictive impact of minor *TP53* variants - update

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BACKGROUND

Current ERIC recommendations (Malcikova et al., *Leukemia 2018*)

- consensus of the experts from ERIC TP53 Network:

→ Report variants ≥10% VAF

→ Report variants 5-10% VAF only if stating that „*the clinical impact of minor subclonal mutations has not been conclusively documented. There is not enough evidence for making therapeutic decisions based on the detection of mutations present in low variant allele frequency*“

- **In clinical trials so far, Sanger sequencing data have been used.**
- **Poor prognosis of all *TP53*-mut cases including those with low-VAF defects were described in some but not all studies.**
- **Predictive impact and risk of minor clone expansion is unclear.**

MAIN ACTIVITIES of this ERIC Multicenter Study

- 1. **METHODICAL HARMONIZATION**

  Inter-laboratory comparison of NGS results obtained from the set of reference samples

- 2. **DATA COLLECTION**

  NGS for *TP53* with detection limit at least 1%

  Consecutive samples of CLL patients entering first-line therapy with follow-up ≥4 years

ORGANIZING TEAM

- **BRNO**, Sarka Pospisilova, Sarka Pavlova and Jitka Malcikova
- **STOCKHOLM**, Richard Rosenquist Brandell and Lesley-Ann Sutton
- **COPENHAGEN**, Carsten Utoft Niemann
- **BELLINZONA**, Davide Rossi
- **MILAN**, Paolo Ghia and Silvia Bonfiglio

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MAJOR AIMS of the study

- **To compare NGS results among laboratories performing NGS detection of *TP53* mutations** in CLL with detection limit of 1% VAF (→ methodical guide, education)
- To clarify the **prognostic and predictive impact of low-VAF *TP53* variants** in patients entering the first-line treatment
- Depending on the results, possibly **update recommendations** on minor *TP53* variant detection, validation and reporting
- *Recognize factors affecting expansion of TP53 mutations (IGHV status, therapy, VAF, cytogenetics)*

SHOULD WE DECREASE 10% CUT-OFF FOR REPORTING TP53 MUTATIONS? IF YES, HOW MUCH?

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MAIN REQUIREMENTS FOR PARTICIPATION

1. Center has ERIC certification for *TP53* mutation analysis
2. NGS methodology for *TP53* mutation analysis with detection limit 1%
3. Laboratories having consecutive samples from CLL patients entering the first-line therapy and analyzed with ultra-deep NGS for *TP53* with sensitivity 1% and below

INCLUSION CRITERIA

- Consecutive set of samples
- Patients entering the first-line therapy
- Corresponding clinical and laboratory data (disease course and routine prognostic markers)
- Minimal follow-up of 4 years (i.e. sampled before 2015)

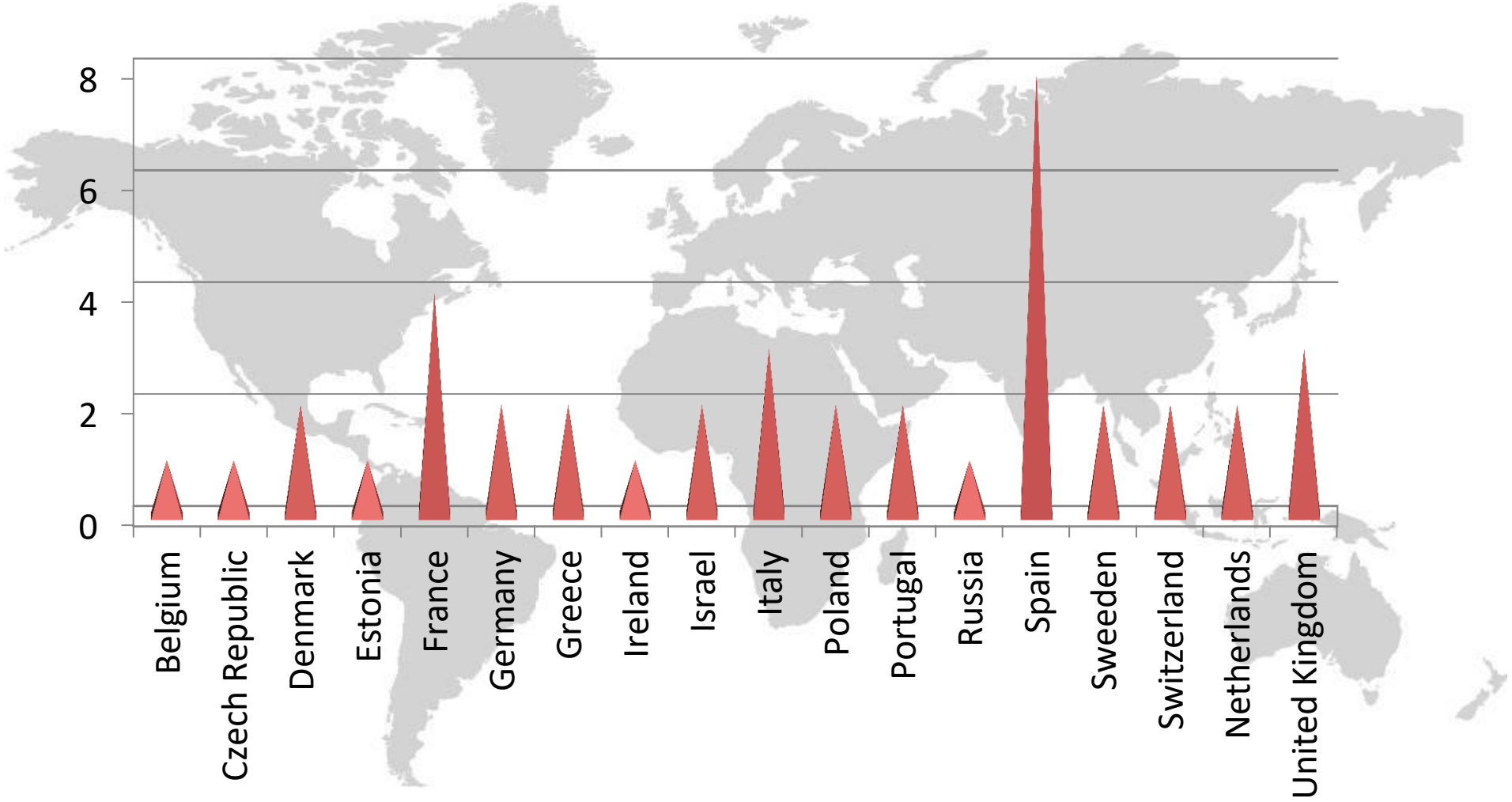
EXCLUSION CRITERIA – AVOIDING UNDESIRABLE BIAS

- The laboratory is not able to perform the NGS analysis reliably within given detection limit and reports significant proportion of false negatives/positives
- Non-consecutive set of samples intentionally enriched for a specific group of patients

CURRENT STAGE OF THE STUDY

- ERIC certified laboratories addressed by ERIC office: end of October 2018
- **41 laboratories responded** (including 5 organizing labs): till 30 November 2018
- Dec 2018-Jan 2019: Discussion on the **selection and preparation of reference samples** among the organizing groups for methodical harmonization
- **7 samples for shipment** in final phase of preparation – samples with variants 1-10% VAF

Participating Laboratories



41 Laboratories from 18 countries

(in total, 144 labs from 28 countries has ERIC certification)

7 of them (41) Methodical harmonization only

ACTIVITIES PLANNED IN THE NEAR FUTURE

- **Reference samples for methodical harmonization (7)**
  to be sent to participating centers via ERIC office

- **Inter-laboratory comparison of NGS results obtained from the set of reference samples**
  Q2-Q3/2019

- **Patient data collection and analysis**
  Collecting data for the study
  Analysis of the data

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THANK YOU VERY MUCH FOR YOUR ATTENTION !

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