WETENSCHAPPELIJK INSTITUUT VOLKSGEZONDHEID
INSTITUT SCIENTIFIQUE DE SANTÉ PUBLIQUE

Centre du cancer
Kankercentrum

# NGS tests and algorithms in (hemato)-oncology

Symposium NGS 2016 | sciensano.be

## ComPerMed

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# Introduction

- Targeted NGS is gradually introduced in molecular diagnostics in daily practice as it enables more precise decision-making:

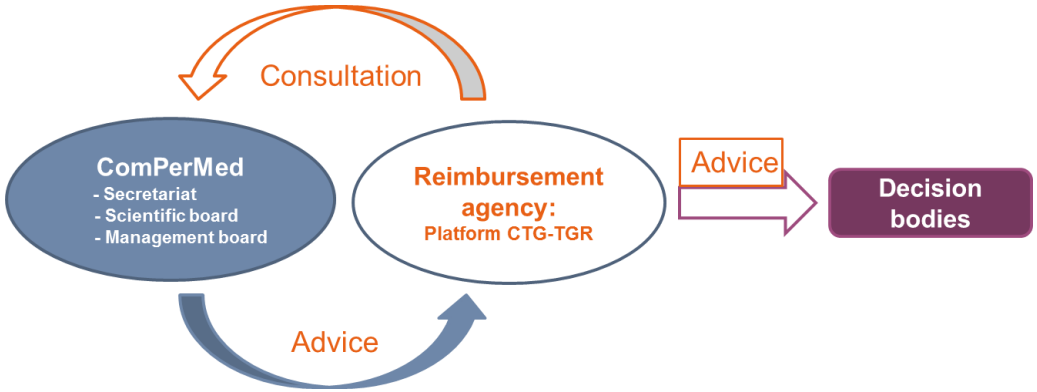
    - diagnosis
    - prognosis
    - therapeutic choices for targeted drugs or conventional treatments

- A permanent monitoring and assessment of the state-of-the-art in this domain is essential

→ Commission of Personalized Medicine (ComPerMed)

# Commission Personalized Medicine (ComPerMed)

- **Aim:** provide evidence-based advices to the platform CTG-TGR of the RIZIV-INAMI
  - technical aspects of NGS testing
  - clinical use of NGS for detecting somatic mutations in cancer patients
  - assessment of novel 'omics' technologies




- Belgian professionals and experts in the field of (hemato)-oncology

# Technical aspects of NGS

NGS guidelines:

→ to **facilitate the implementation** of NGS in the laboratories

→ to help labs to **generate accurate NGS data**
e.g. Identical sample analysis should lead to an identical list of variants even if processed by a different operator on a different day.

→ to **facilitate the evaluation by the auditors** from the accreditation bodies (Belac)

BJMO PRACTICE GUIDELINES 56

## The Belgian next generation sequencing guidelines for haematological and solid tumours

A. Hébrant, Ir, PhD[1], G. Froyen, PhD[2], B. Maes, MD, PhD[2], R. Salgado, MD[3], M. Le Mercier, PhD[4], N. D'Haene, MD, PhD[4], S. De Keersmaecker, PhD[5], K. Claes, PhD[6], J. Van der Meulen, PhD[6], P. Aftimos, MD[7], J. Van Houdt, PhD[8], K. Cuppens, MD[9], K. Vanneste, PhD[5], E. Dequeker, PhD[8], S. Van Dooren, PhD[10], J. Van Huysse, MD[11], F. Nollet, PhD[12], S. van Laere, PhD[13], B. Denys, MD[12], V. Ghislain[14], C. Van Campenhout, PhD[14], M. Van den Bulcke, PhD[1]

Belg J Med Oncol 2017 Apr 1;11(2):56-67

# Clinical use of NGS

Selection of genes with regard to their **test utility** for a specific tumor

→ **diagnosis**

→ **therapeutic** response (to predict **sensitivity** or **resistance**)

→ **prognosis** (patient outcome)

→ **biomarker/test levels**

**Level 1**

- Standard of care biomarker for diagnosis and/or prognosis *
- Biomarker predictive of a response or a resistance to a reimbursed drug in Belgium for this indication

**Level 2**

**A**

- Recommended standard of care biomarker for diagnosis and/or prognosis +
- Biomarker predictive of response or resistance to an EMA-approved drug for this indication

**B**

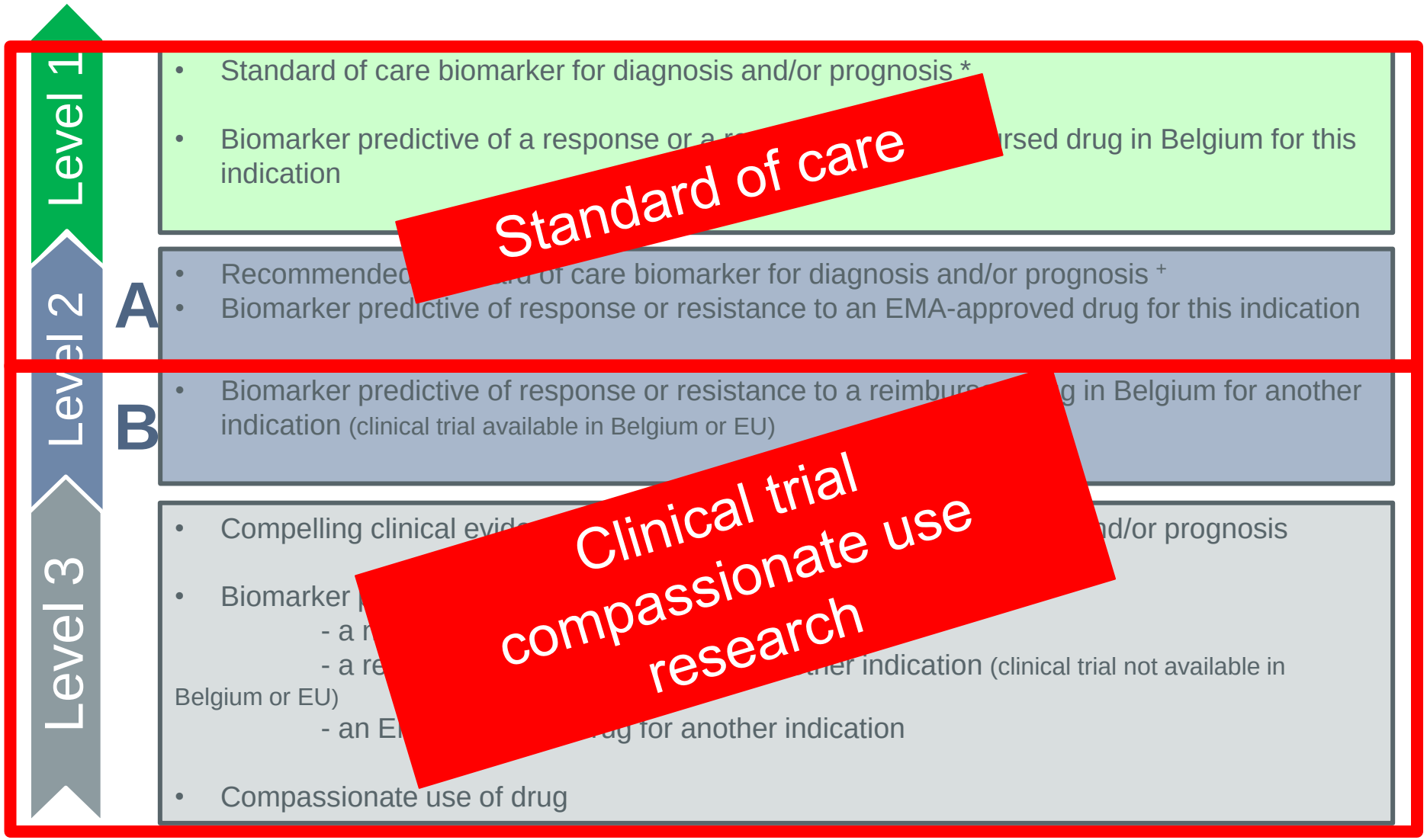
- Biomarker predictive of response or resistance to a reimbursed drug in Belgium for another indication (clinical trial available in Belgium or EU)

**Level 3**

- Compelling clinical evidence supporting the biomarker for diagnosis and/or prognosis
- Biomarker predictive of a response or a resistance to
  - a non EMA-approved drug in this indication
  - a reimbursed drug in Belgium for another indication (clinical trial not available in Belgium or EU)
  - an EMA-approved drug for another indication
- Compassionate use of drug

* Standard of care: Included in guidelines (WHO) AND consensus from experts ComPerMed

+ Recommended standard of care: Clinical evidence AND consensus from experts ComPerMed

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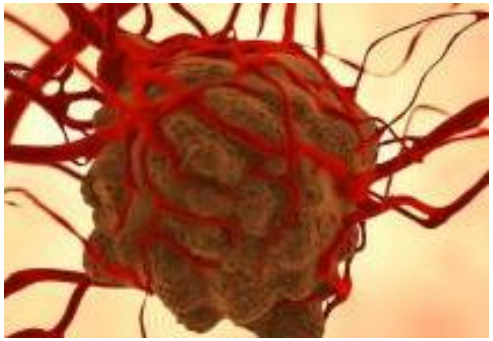
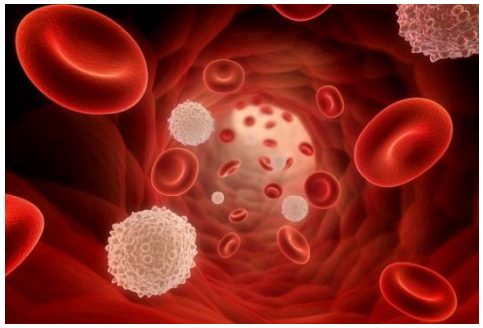
# Clinical use of NGS

**Test utility and level**

Solid tumors



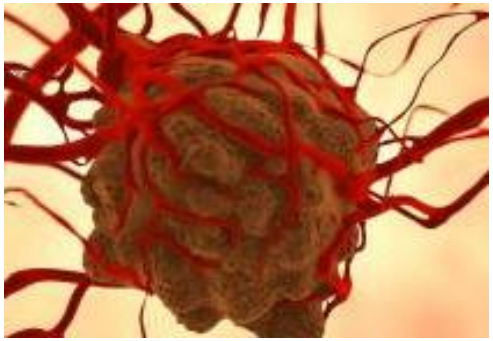
Hematological tumors



# Clinical use of NGS

**Test utility and level**

Solid tumors



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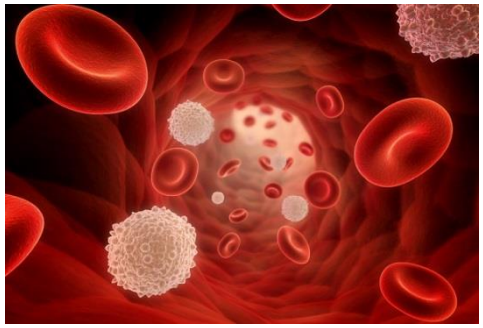
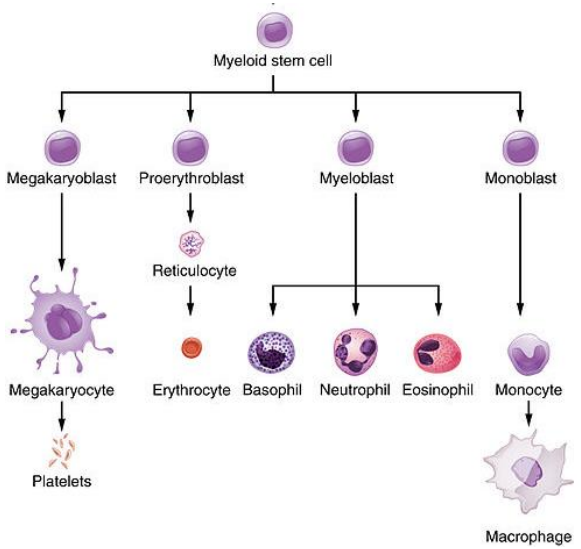


MYELOID CANCERS

# Clinical use of NGS

List of myeloid cancers for which an NGS test is useful:

- Acute myeloid leukemia (AML)
- Myeloproliferative neoplasm (MPN)
  - Chronic neutrophilic leukemia (CNL)
  - Primary Myelofibrosis (PMF)
- Myelodysplastic syndrome (MDS)
- MDS/MPN
  - Chronic myeolomonocytic leukemia (CMML)
  - Atypical CML (aCML)
  - MDS/MPN-RS-T



# Clinical use of NGS

List of genes which should be analyzed at minimum by NGS: level 1 & 2A

| Acute myeloid leukemia | | | |
|---|---|---|---|
| **Genes** | **Diagnosis** | **Prognosis** | **Therapy** |
| ASXL1 | x (2A) | x (1) | |
| CEBPA* | x (1) | x (1) | |
| DNMT3A* | x (2A) | x (1) | |
| FLT3 | x (2A) | x (1) | x (2B) |
| IDH1 | x (2A) | x (1) | x (3) |
| IDH2 | x (2A) | x (1) | x (3) |
| KIT | x (2A) | x (1) | x (2B) |
| NPM1 | x (1) | x (1) | |
| RUNX1* | x (1) | x (1) | |
| TET2* | x (2A) | x (1) | |
| TP53* | x (2A) | x (1) | x (3) |
| WT1 | x (2A) | x (1) | |

# Clinical use of NGS

List of genes which should be analyzed at minimum by NGS: level 1 & 2A

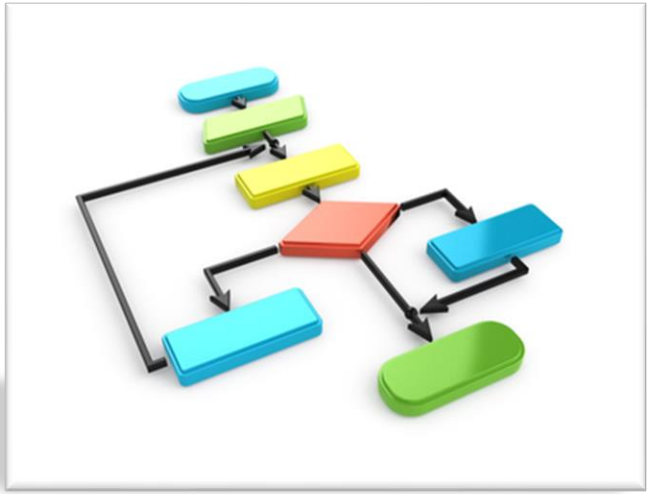
| Genes | AML | MDS | MPN PMF | MPN CNL | MDS/MPN aCML | MDS/MPN CMML | MDS/MPN RS-T |
|---|---|---|---|---|---|---|---|
| ASXL1 | x | x | x | x | x | x | |
| CALR | | | x | | x | | x |
| CEBPA | x | | | | | | |
| CSF3R | | | | x | x | | |
| DNMT3A | x | x | | | | | |
| EZH2 | | x | x | | | | |
| FLT3 | x | | | | | | |
| IDH1 | x | | x | | | | |
| IDH2 | x | | x | | | | |
| JAK2 | | | x | | x | | x |
| KIT | x | | | | | | |
| MPL | | | x | | x | | x |
| NPM1 | x | | | | | | |
| RUNX1 | x | x | | | | | |
| SETBP1 | | | | x | x | x | |
| SF3B1 | | x | x | | | | x |
| SRSF2 | | x | x | x | x | x | |
| TET2 | x | x | x | x | | x | |
| TP53 | x | x | | | | | |
| U2AF1 | | x | | | | | |
| WT1 | x | | | | | | |

# Clinical use of NGS

Algorithms

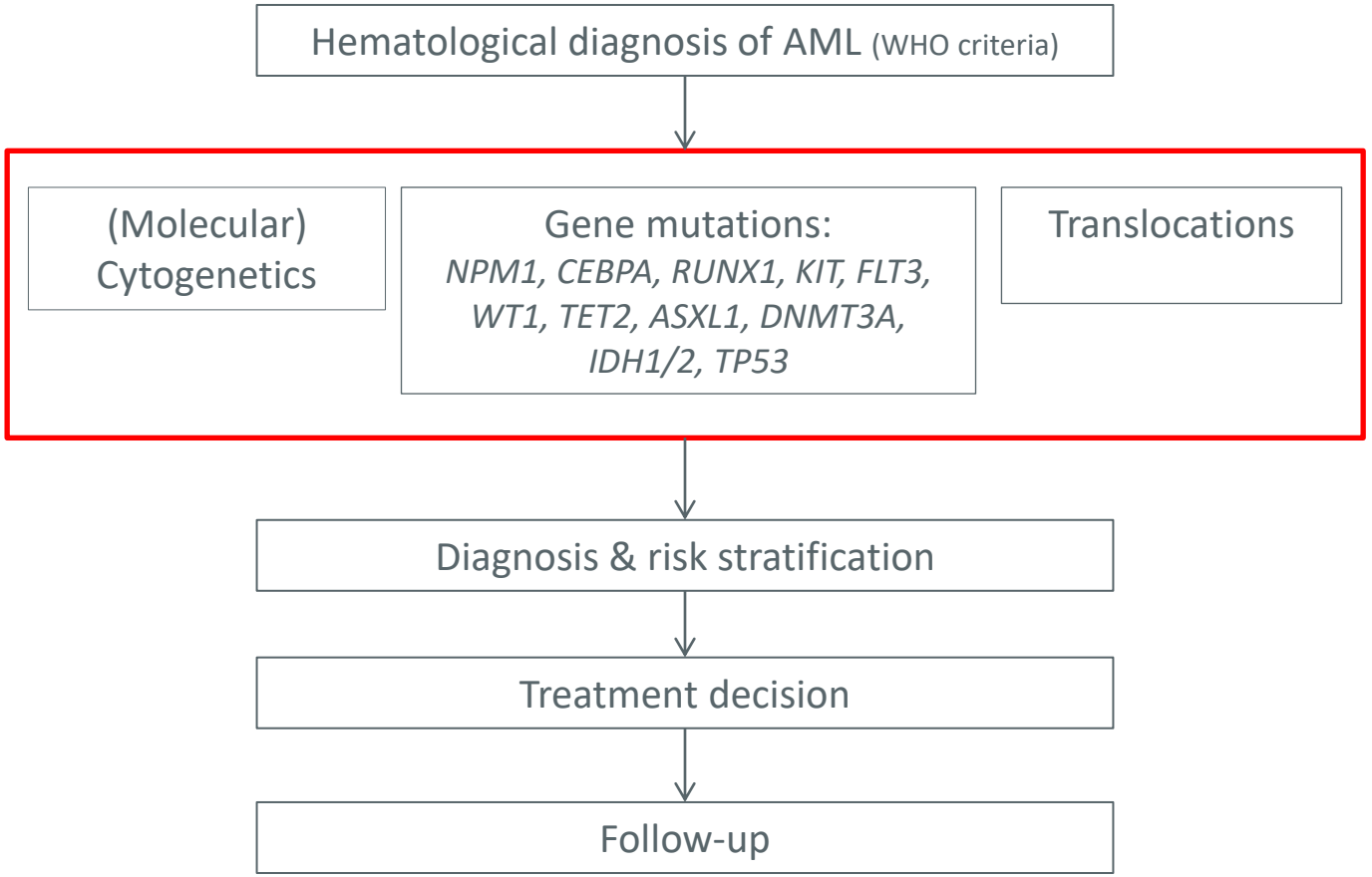
→ Display the NGS test in the context with all the other molecular tests (FISH, IHC, PCR,…)

→ Define the indications for NGS testing



# Clinical use of NGS

Example: algorithm of acute myeloid leukemia



# Clinical use of NGS

Integrate NGS testing and algorithm in a website

# Clinical use of NGS

Integrate NGS testing and algorithm in a website

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## Algorithms

- Incidence
- List of experts
- Algorithms

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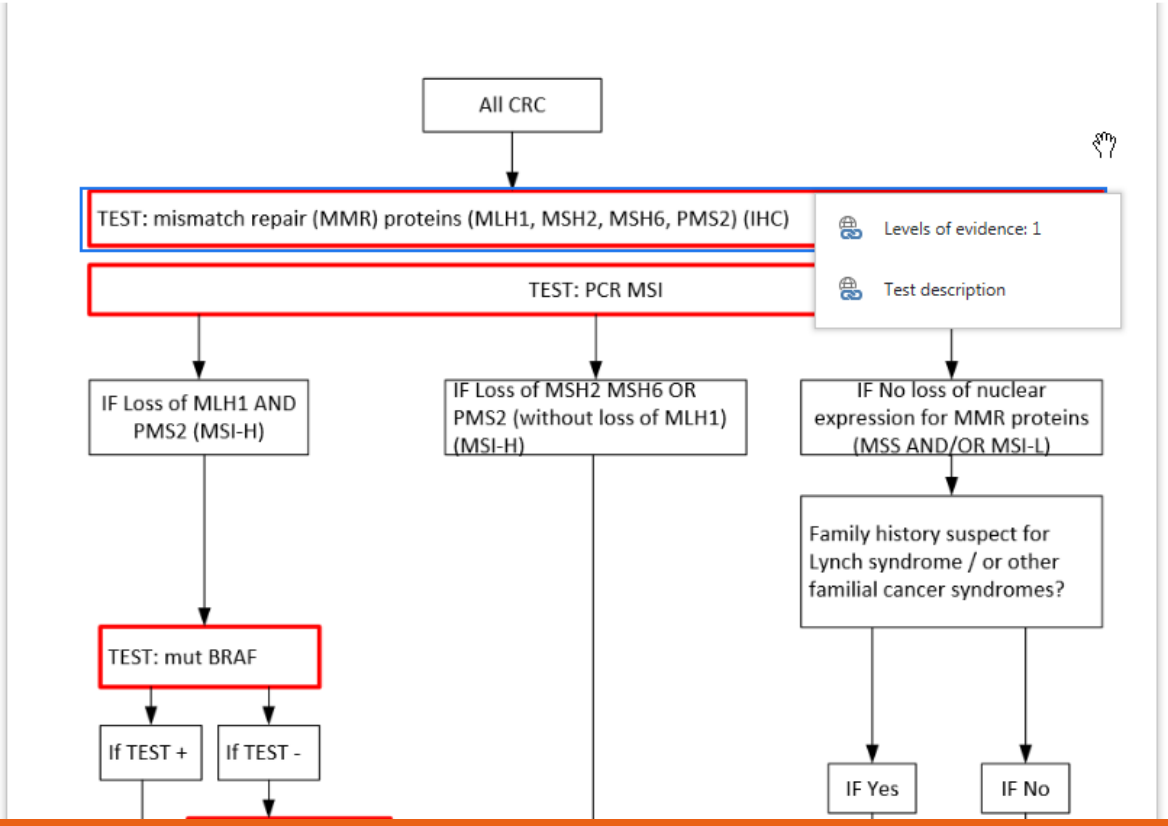

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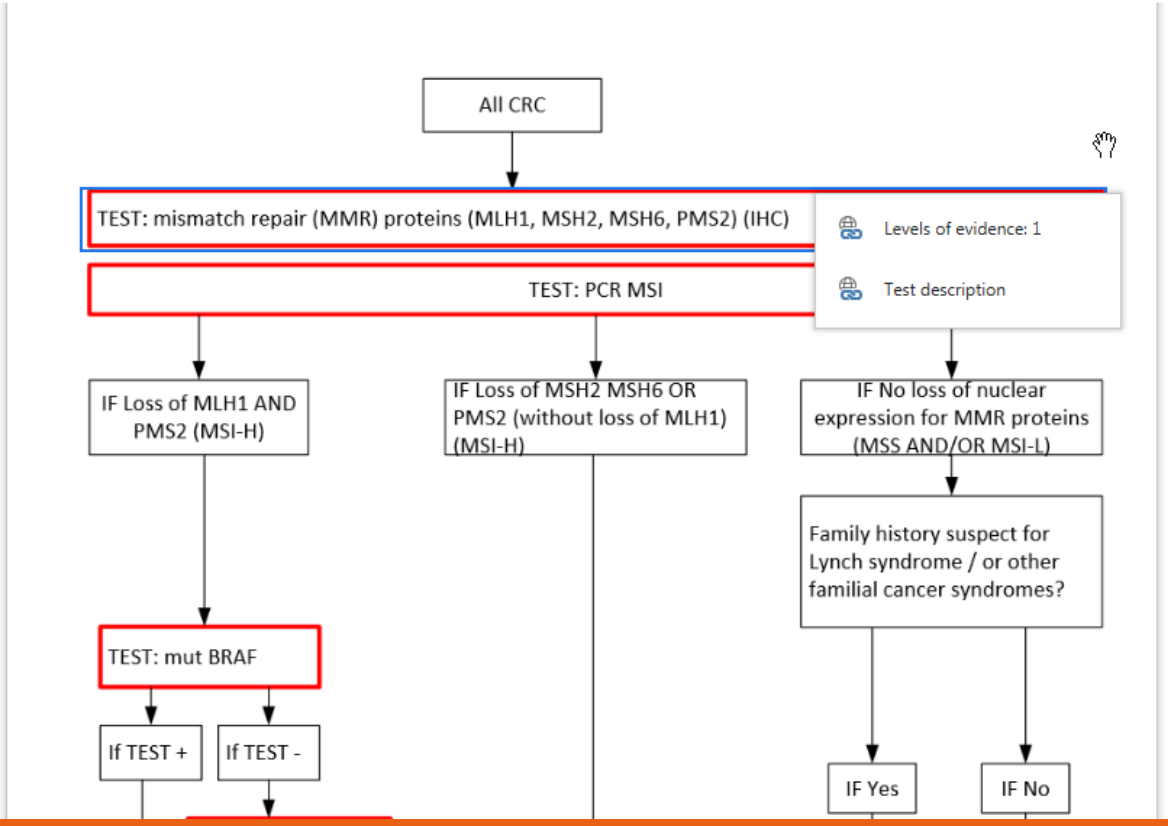

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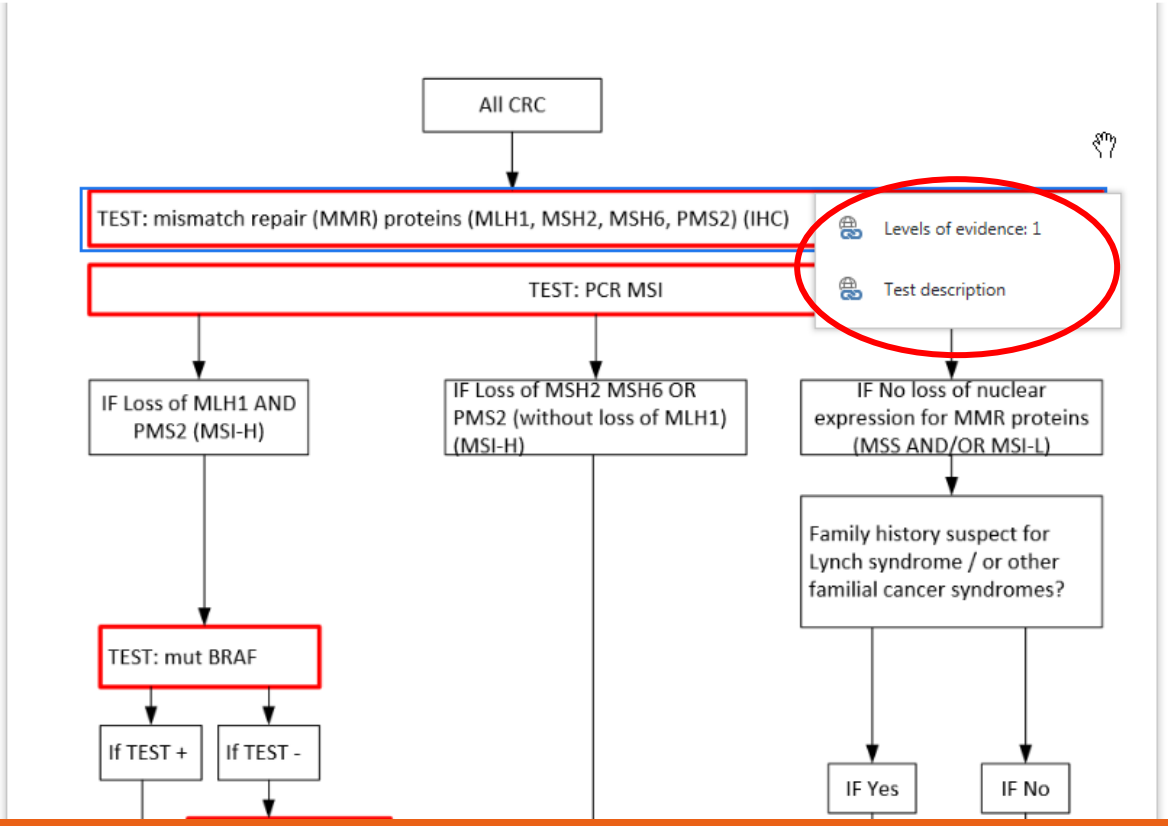


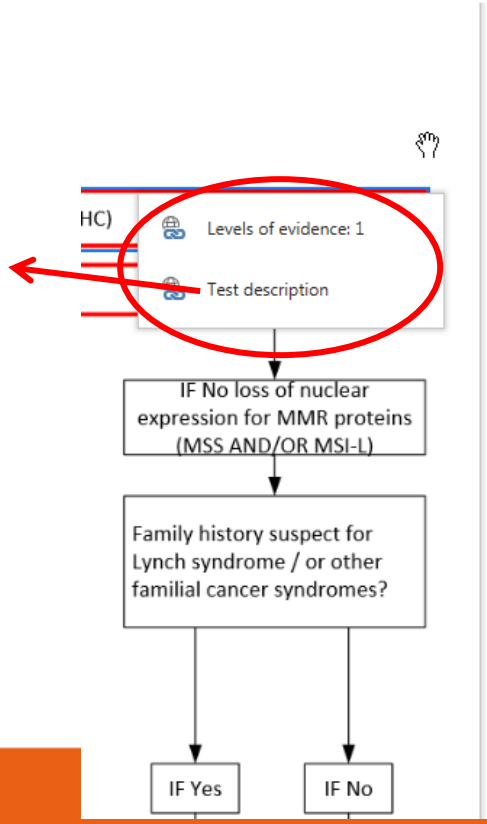
# Clinical use of NGS

Integrate NGS testing and algorithm in a website

MMR proteins test by IHC and/or PCR MSI in CRC

Microsatellite instability (MSI) is a hypermutable phenotype caused by the loss of DNA mismatch repair activity. Microsatellites are non-coding DNA sequences constituted by repeated units of 2-9 base pairs. They are randomly dispersed throughout the human genome. Microsatellite instability (MSI) is defined as a change (deletion or insertion of repeating units) in the microsatellite sequences in a tumor compared to the normal tissue. Microsatellite instability (MSI) is caused by a defect in the DNA mismatch repair (MMR) genes which normally occurs to correct errors during DNA replication.

The PCR detection by the amplification of 5 mono/di-nucleotide microsatellite markers is the standard test. MSI tests can be divided into three groups: MSI-H, when ≥ 30% of markers exhibit



# Future work

- Website: January 2018
- Regularly update clinical use of NGS: genes and algorithms
- Clinical use of NGS in other hematological cancers (lymphoid)
- Clinical use of NGS in pediatric cancers
- Harmonize variant annotation and clinical interpretation

# THANK YOU