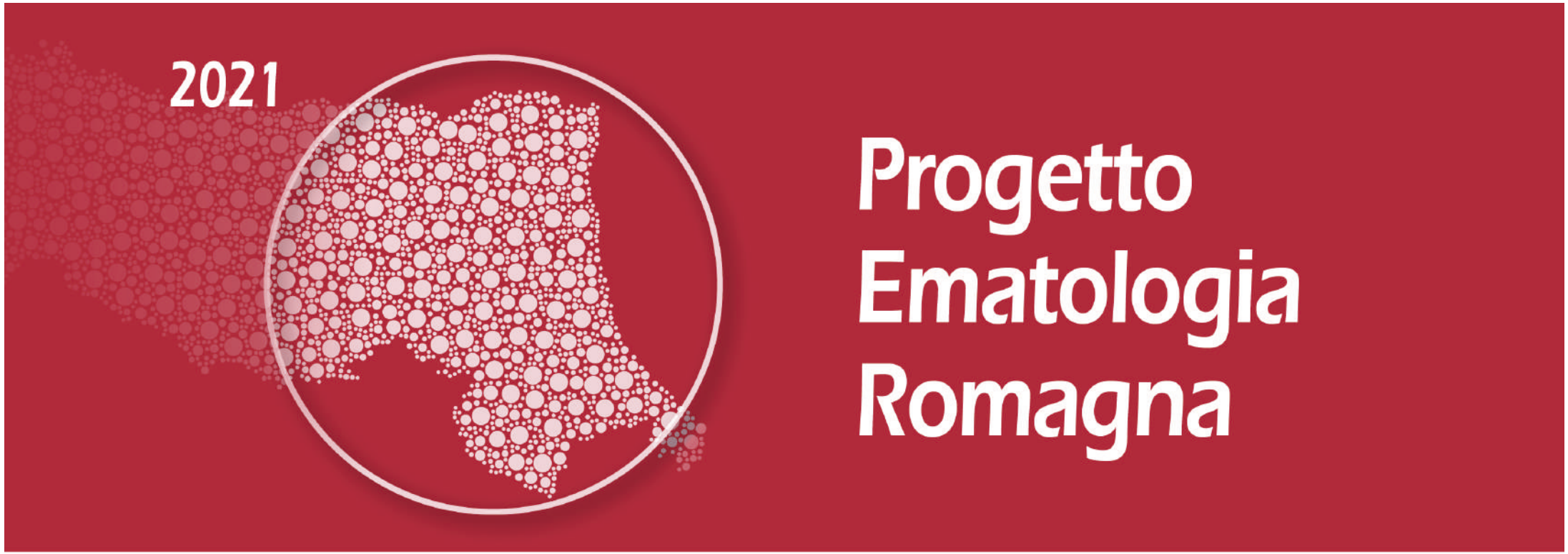


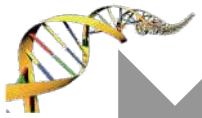
Dallo studio del genoma una terapia senza citotossici in ematologia: sogno o realtà?

Simona Soverini

2021

Omics as the key to precision medicine?

The promises of omics technologies



DNA

Epigenomics

Genomics

RNA

Transcriptomics

proteins

Proteomics

New biological insights

- Molecular pathogenesis
- Diagnosis and risk classification
- Personalized treatment??

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ARTICLES

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

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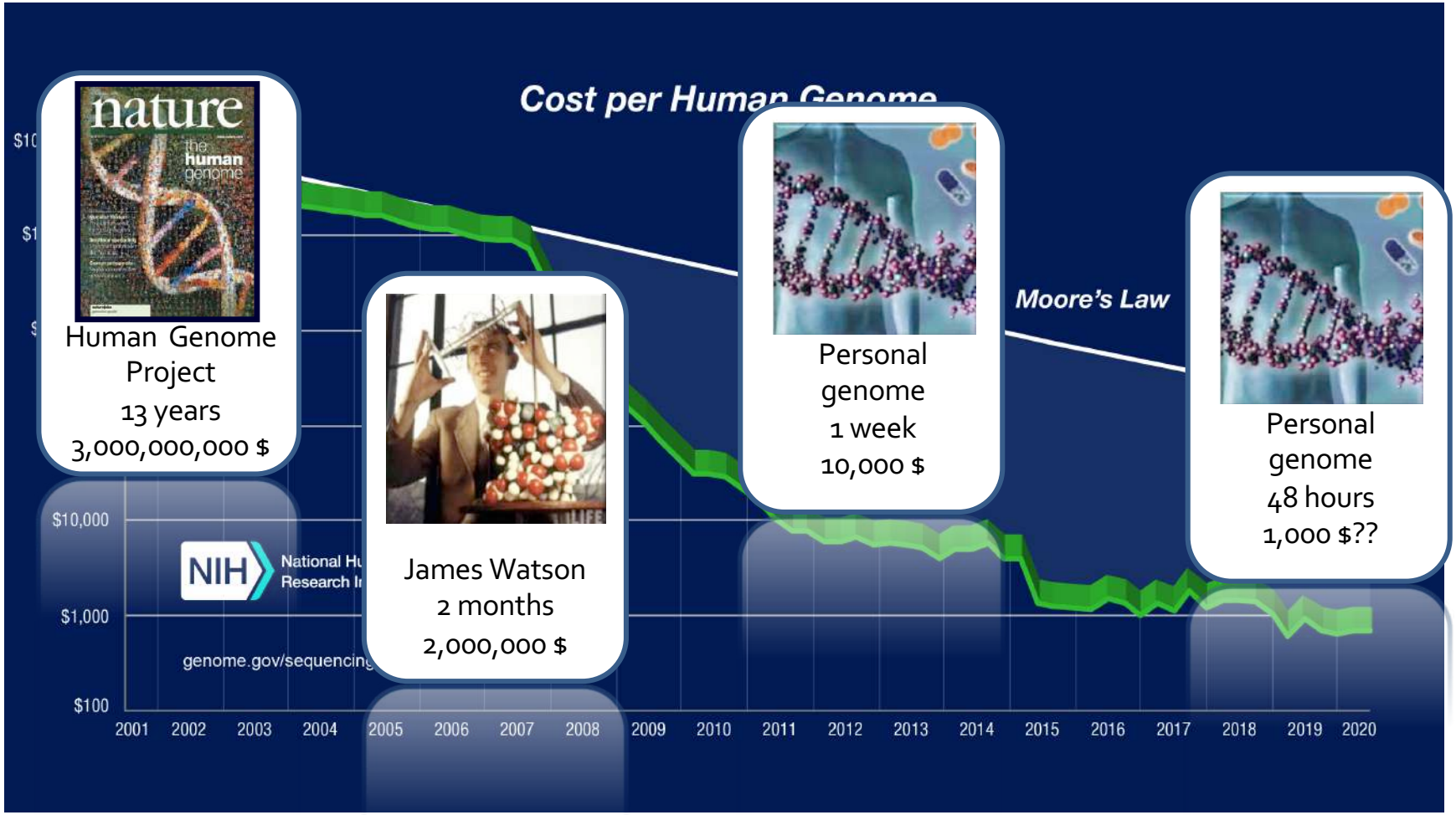
Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient's skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse, the function of which is not yet known. Our study establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.

Genomics becoming affordable



Routine genomics feeding personalized therapy: are we there yet?

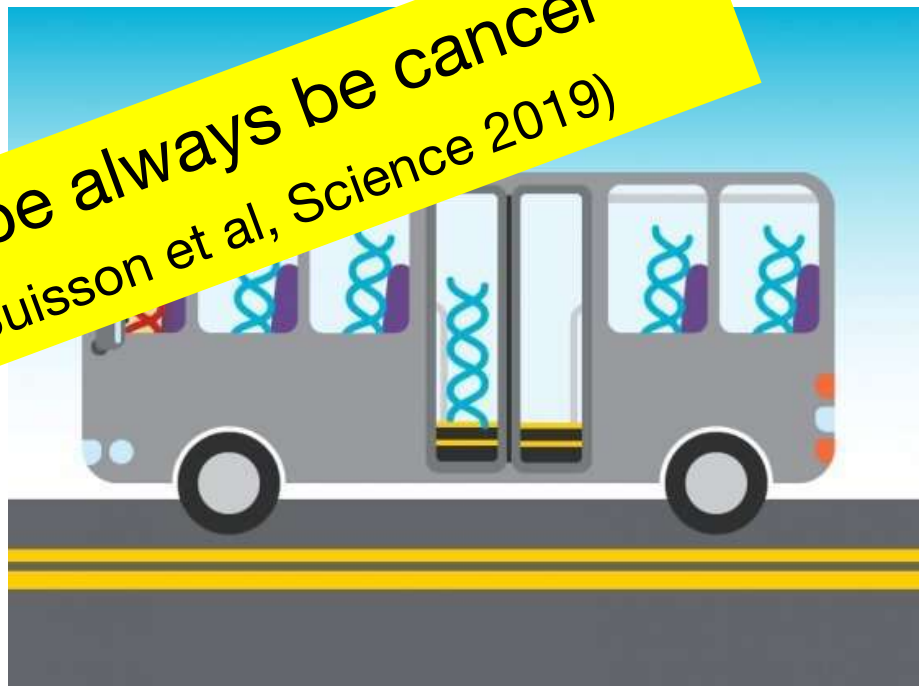
Discriminating driver vs passenger mutations

DRIVER mutations → are causally implicated in oncogenesis

vs

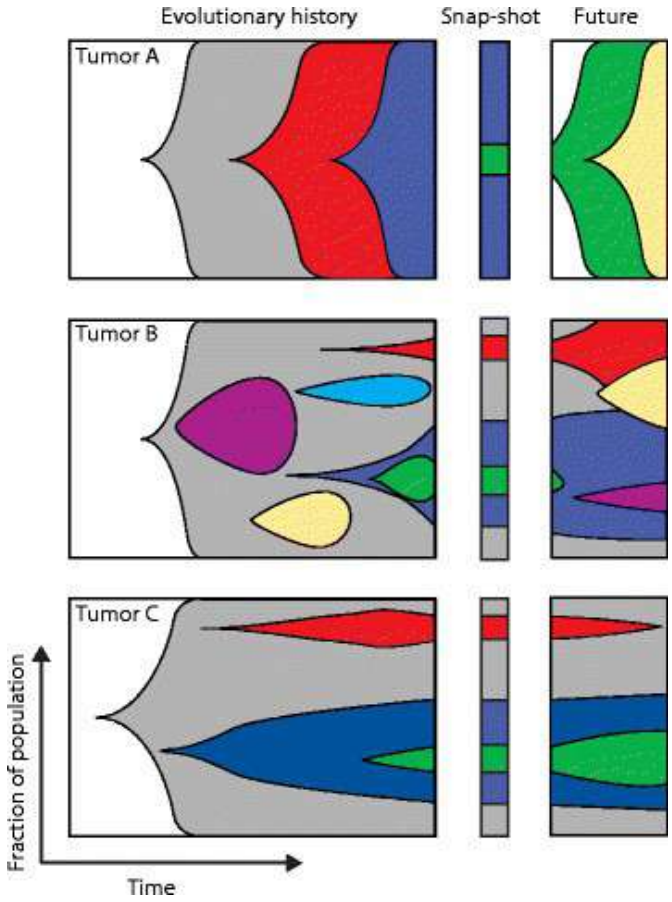
PASSEN… carried … in the clonal expansion

mutation hotspots may not be always be cancer drivers and drug targets! (Buisson et al, Science 2019)



Coping with tumor heterogeneity

- The bulk tumour may be a collection of diverse subclones harbouring distinct molecular signatures with differential levels of sensitivity to treatment, following distinct evolutionary trajectories over time (INTRA-TUMOR HETEROGENEITY)
- The same tumor type may result from different mutations or combinations of mutations in different patients (INTER-TUMOR HETEROGENEITY)

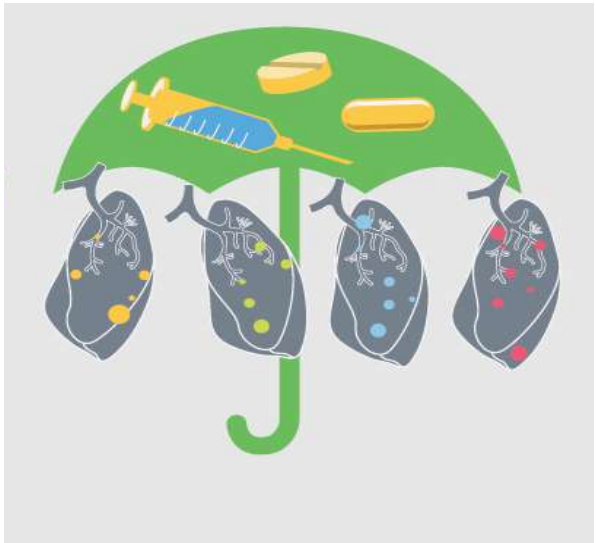


Finding and acting on actionable mutations

- Some lesions are undruggable (e.g., the loss of function of a tumor suppressor)
- Some lesions may not have yet an approved targeted therapy
- Off-label use of targeted agents and drug repurposing not always easy

'Umbrella' trials

Different drugs are tested against multiple genetic mutations within the same cancer type



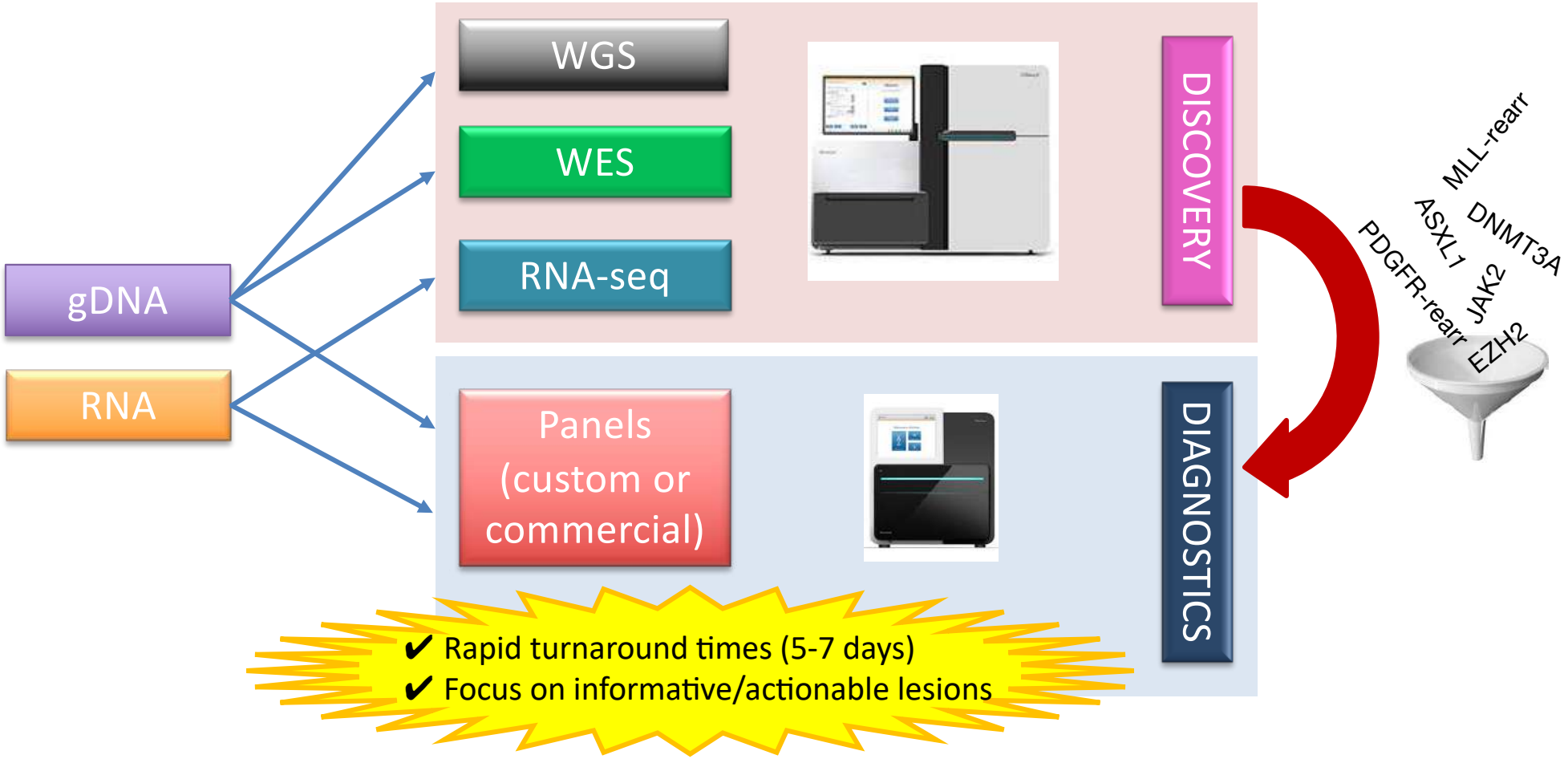
'Basket' trials

One drug is tested against a particular genetic mutation across different cancer types

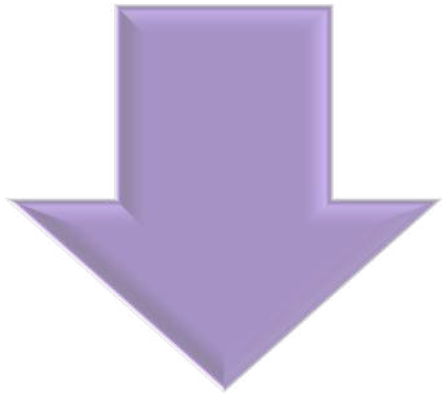
Dealing with data & information overload

- Handling, storing, analyzing and visualizing results is not trivial
- Reporting only clinically relevant alterations in a clinically relevant time frame
- Incidental findings?

2021 Targeted panels for routine genomic assessment



And the winner will be……..?



Mutation-specific therapeutic approach

Mutation-agnostic therapeutic approach

12.00 – 13.30 **DALLO STUDIO DEL GENOMA UNA TERAPIA SENZA CITOTOSSICI IN ONCOEMATOLOGIA: PROMESSA O REALTÀ?**

Introduzione	*S. Soverini*
Nelle leucemie mieloidi acute	*C. Papayannidis*
Nelle leucemie linfoblastiche acute	*S. Chiaretti*