Opportunities for CDG diagnostics

Dulce Quelhas
Unidade de Bioquímica Genética
Centro de Genética Médica Jacinto de Magalhães
Centro Hospitalar Universitário do Porto
dulce.quelhas@chporto.min-saúde.pt

CDG
Congenital Disorders of Glycosylation

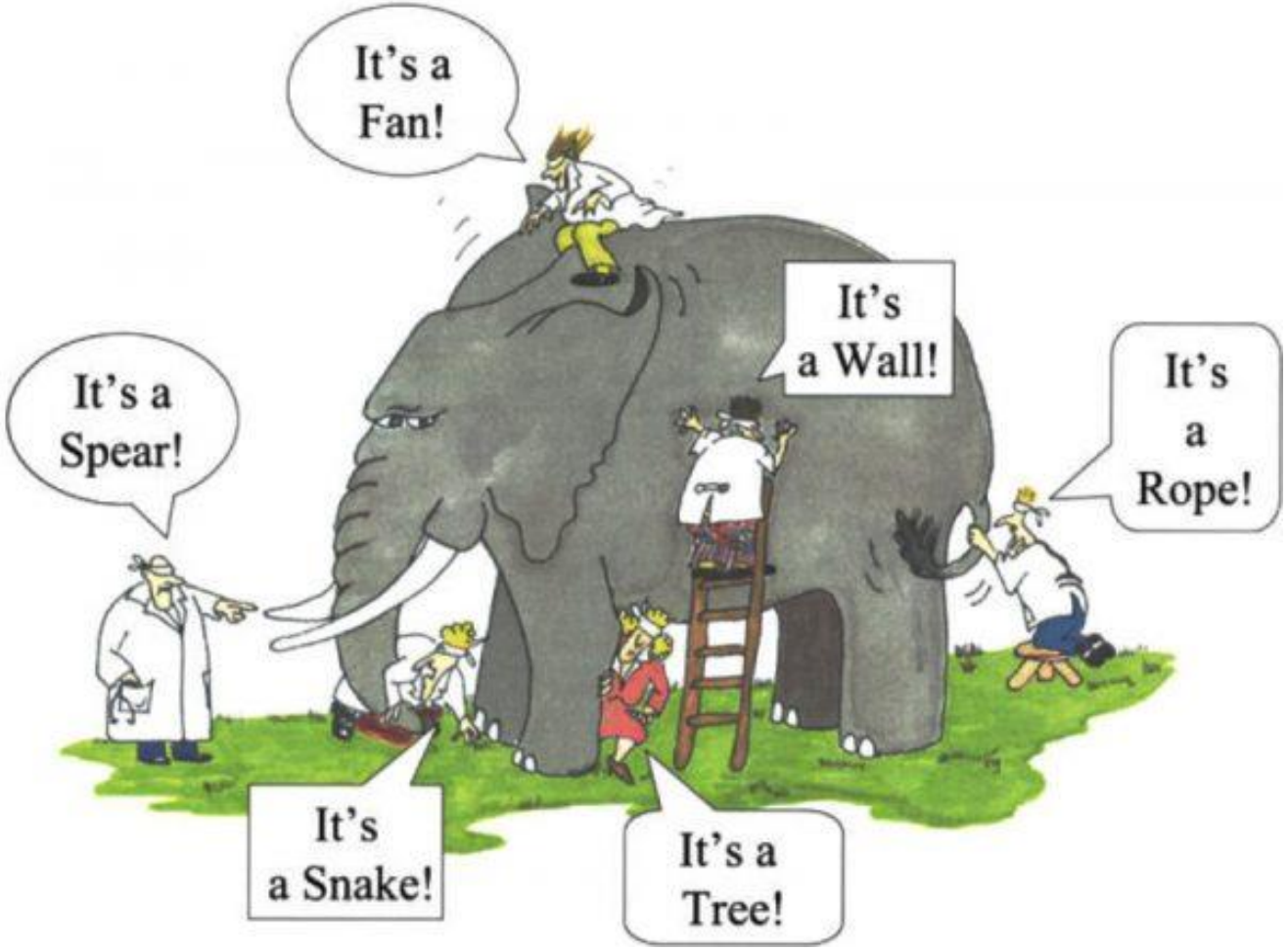
centro hospitalar do Porto

CGM Centro de Genética Médica Doutor Jacinto Magalhães

UMIB

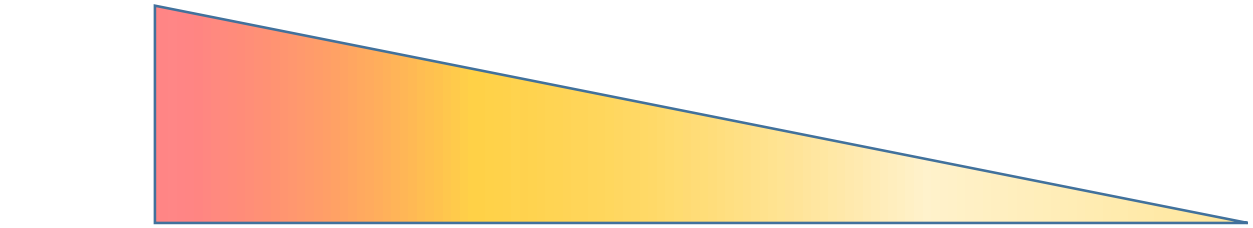
Congenital Disorders of Glycosylation

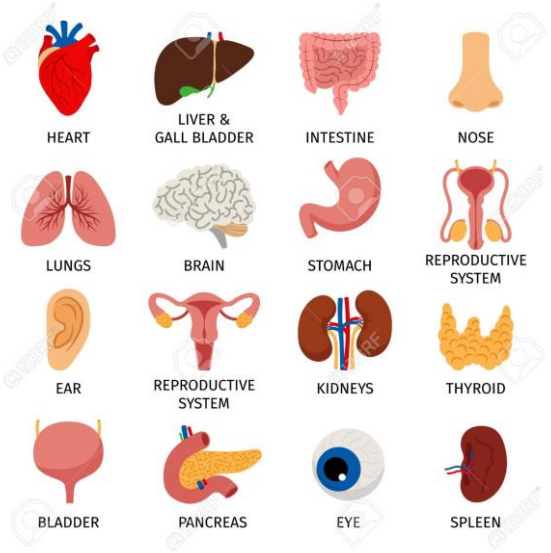
Rare disorders



CDG diagnosis today

- **Clinical**
  - phenotype from Greek *phainein* to show + *typos* type
  - Multisystemic disorder/Specific organ affected

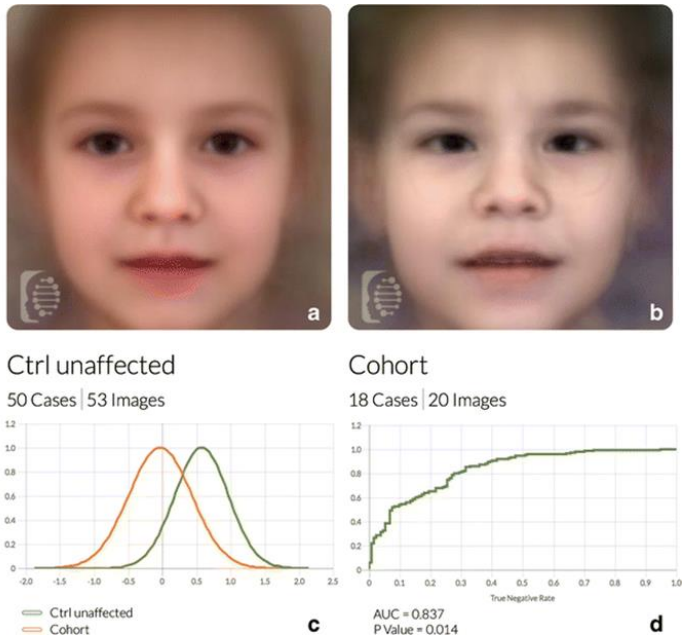




Depends on clinician (teams) experience/knowledge on CDG, sometimes only available in specialized centers

Congenital Disorders of Glycosylation

CDG diagnosis



Face2gene *https://doi.org/10.1007/s10545-018-0156-5<*

J Child Neurol. 2019 Jun;34(7):410-414. doi: 10.1177/0883073819833543. Epub 2019 Mar 11.

Unusual Presentation of PMM2-Congenital Disorder of Glycosylation With Isolated Strokelike Episodes in a Young Girl.

Farmania R[1], Jain P[1,2], Sharma S[3], Aneja S[3,4].

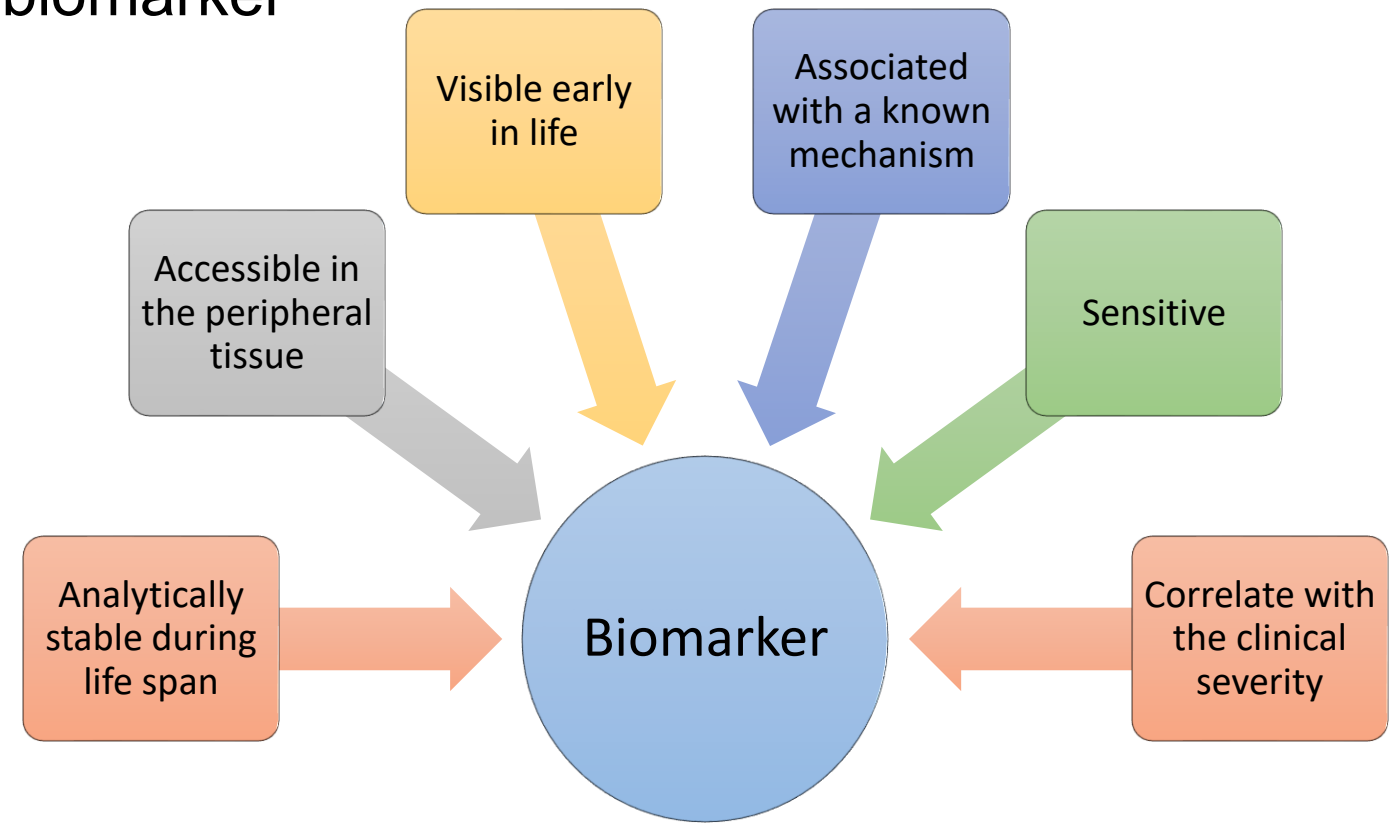
Author information

«“…a developmentally normal young girl who presented with isolated stroke like episodes and was diagnosed to have PMM2-CDG. This condition should be kept in the differentials of unexplained stroke like episodes in children.”

Future - Integrated artificial intelligence/ clinical decision tools

CDG diagnosis

- **Biochemical**
  - Concept of “Ideal biomarker”



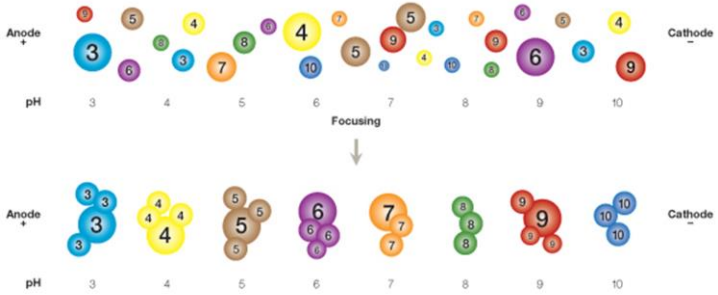
Congenital Disorders of Glycosylation

CDG diagnosis
Complementary CDG biomarkers

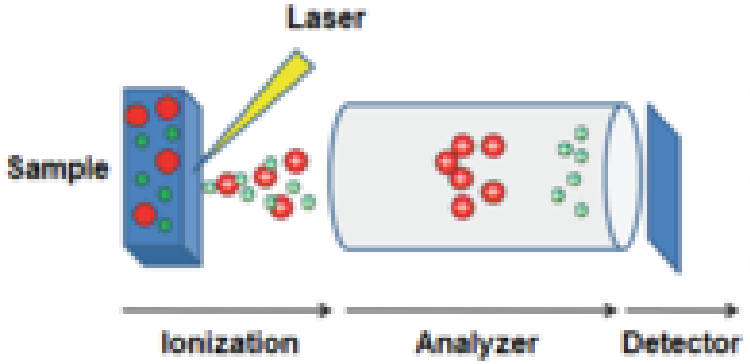
- ↓Antithrombin III
- ↓Protein C
- ↓Protein S
- ↑PTT
- ↑PT
- ↓ factor IX activity
- ↓ factor XI activity
- ↑ hepatic transaminases
- Hypoalbuminemia
- ↓ thyroxin-binding globulin
- ↑ thyroid-stimulating hormone
- Proteinuria
- ↓ IgA
- ↓IgG
- Abnormal circulating cholesterol
- Hyperinsulinemia
- Thrombocytopenia
- Insulin resistance
- ↓ Ceruloplasmina
- ↓Manganês
- ↓ Zinc

CDG biochemical diagnosis

- Transferrin /N-glycosytalion
  - ✓ Isoelectric Focusing
  - ✓Capillary Zone Electrophoresis
- O-glycosylation – Apo CIII Isoelectric Focusing



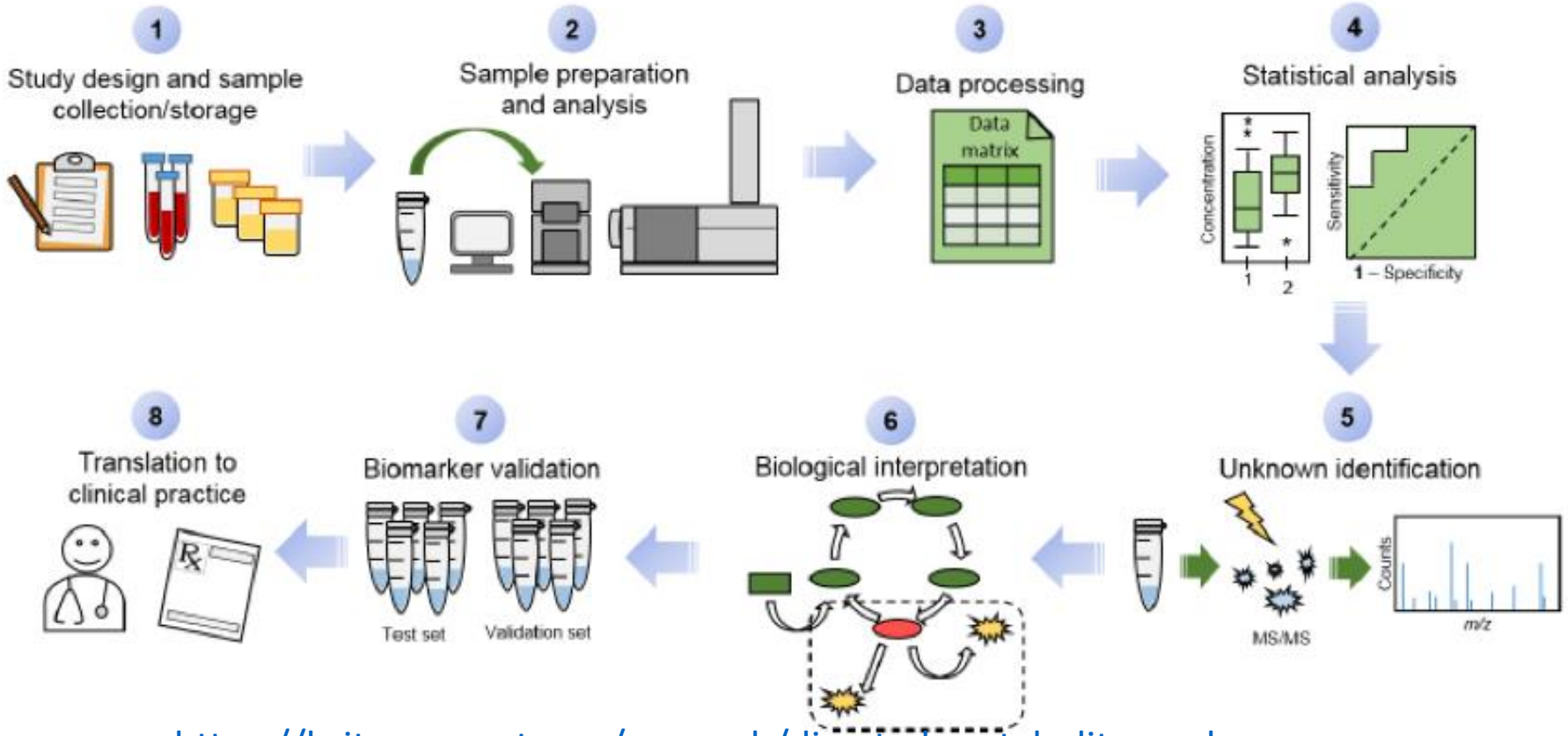
- Glycoproteins, transferrin included
  - ✓MALDI-TOF
    - **M**atrix-**A**ssisted **L**aser **D**esorption/**I**onization)
    - **T**ime-**O**f-**F**light mass spectrometer)



https://commons.wikimedia.org/wiki/File%3AMALDI-TOF_MS.png

Congenital Disorders of Glycosylation

Metabolomics for new biomarkers



https://britz.mcmaster.ca/research/directed-metabolite-analyses

Congenital Disorders of Glycosylation

The classical approach

Clinical phenotype

Biochemical screening tool
- -Transferrin Isoeletric focusing
- - LLO, Glycan analysis…

Molcular genetics analysis - Sanger sequencing

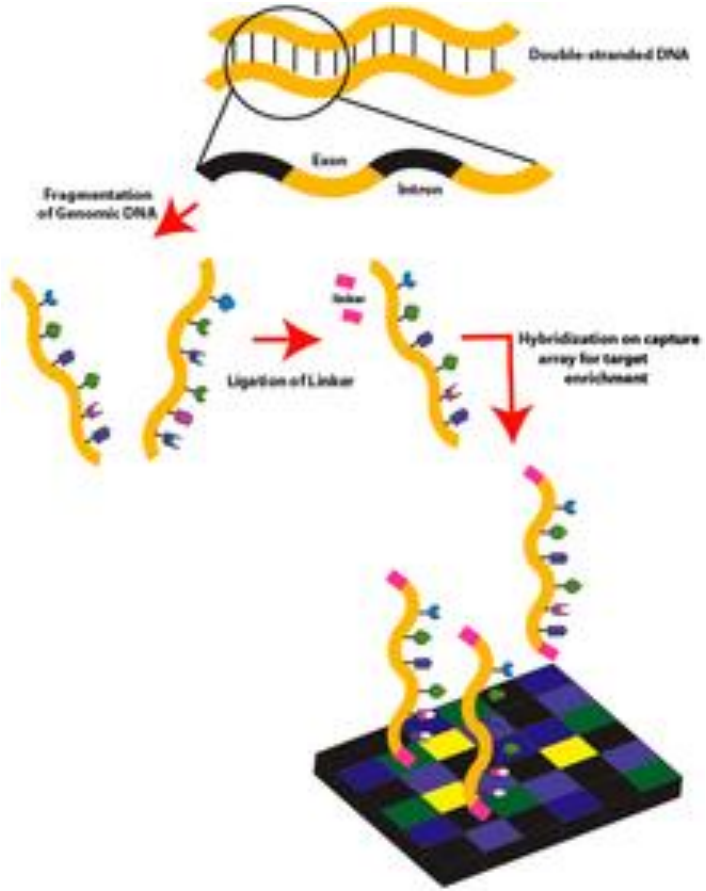
CDG diagnosis

Massively parallel sequencing changed genetics diagnosis

Clinical phenotype – unspecific or without most significant signs/symptoms

Clinical exome/ Whole Exome Sequencing
Pathogenic vs unknow significant variants

Biochemical confirmation



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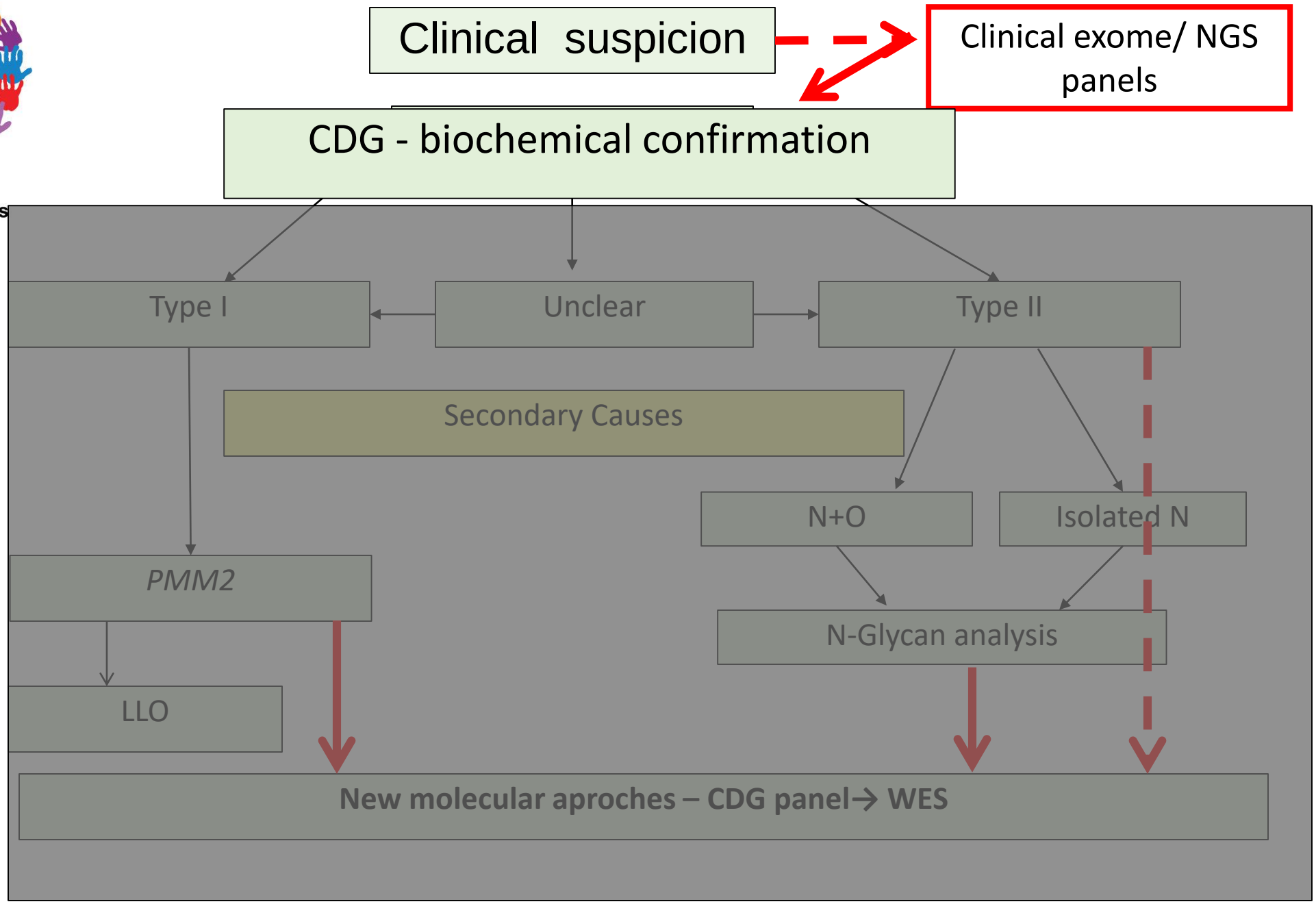
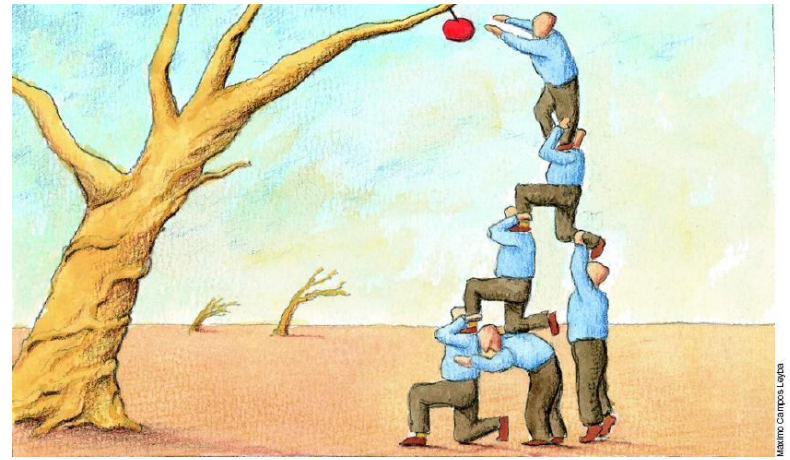


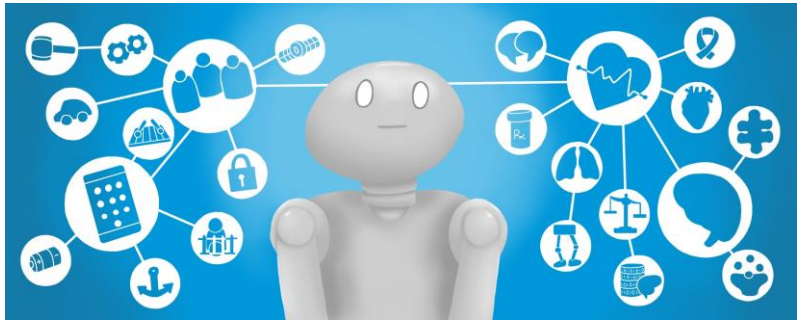
How can diagnosis guide clinical care?

- Early diagnosis can alter outcomes
  - Treatment specific signs and symptoms
  - Complementary clinical and social support
    - Physiotherapy
    - Prompt stimulation
    - Social support
    - Design of adapted school curricula
    - Social integration of patients and families

Challenges for the future

- Collaborative work of all the stakeholders
- Awareness – ongoing process
- Metabolomics studies in large cohorts
  - New biomarkers
  - Important for new therapies
  - Treatment monitoring
- Genomics will increased broadness of clinical phenotype
  - Artificial intelligence / combined diagnostic databases





https://news.stanford.edu/2018/05/15/how-ai-is-changing-science/

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