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Discussion on:

What is the Screening Target? Presented by Uri Ladabaum

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The challenge

- Screening target; early cancers and precursor lesions at risk to progress to cancer.
- Which precursor lesions are at risk of progressing? The natural history of progression of these lesions is interrupted.
- The currently used high risk lesion (advanced adenomas or advanced sessile serrated polyps) is not ideal as a substantial proportion of these would not progress to cancer if not resected.
- Using these clinical-histological features as surrogate of risk of progression leads:
    - To overdiagnosis and overtreatement.
    - To underestimation of the performance of screening tests.

How to move forward

- Molecular changes involved in the progression to cancer should be more accurate to determine the risk of progression of a certain precursor lesion.

- Cross-sectional studies analyzing precursor lesions that have proven to have progressed (e.g. malignant polyps) help identifying the molecular changes associated with adenoma-to-carcinoma progression.

- Therefore, the path forward should:

    - Incorporate progression-associated molecular changes as biomarkers in new screening tests (**screening markers**).

    - Use progression-associated molecular changes as surrogates of risk of progression in the evaluation of the performance of screening tests (**intermediate endpoints**).

Current status

- There is evidence that the occurrence of chromosomal instability (CIN) plays an important role in the transition to malignancy

(Hermsen et al, Gastroenterology 2002; Matano et al, Nat Med 2015; Saito, Nat Commun 2018)

- Specific chromosomal copy number aberrations (CNAs) were associated with colorectal adenoma-to-carcinoma progression.

(Hermsen et al, Gastroenterology 2002; Carvalho et al, Gut 2009)

- Existence of pre-clinical models (organoids) that mimic the natural history of adenoma-to-carcinoma progression.

(Matano et al, Nat Med 2015; Drost et al, Nature 2015; Kawasaki et al, Gastroenterology 2019; own unpublished data)

Conclusion

There is enough evidence showing that molecular markers (e.g. CNAs) better reflect the biology of progression and therefore could, in the future, be explored:

- as **markers in new screening tests** (we are not there yet)

  Detection of CNAs in body fluids (e.g. blood, stool) is possible but not yet technically feasible, especially regarding early stages of disease (including precursor lesions).

  (Leary et al, Sci Transl Med 2012)

- as **intermediate endpoints**:

  Time to consider molecularly-defined high-risk adenomas as intermediate endpoints in the evaluation of (new) screening tests in population screening studies (in comparison to the classic advanced adenoma intermediate endpoint).

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