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 overtreatment.
  • 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.
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).