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Potential for optimizing fecal immunochemical test−based colorectal cancer screening strategies

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Colorectal cancer (CRC) is a common, yet largely preventable cancer. Colonoscopy, despite its high effectiveness in detecting CRC and its precursors, advanced adenomas (AAs) and non-advanced adenomas, cannot be seen as ideal CRC screening modality. Adherence rates to colonoscopy screening are limited. Within the initial 10 years from introduction of screening colonoscopy in Germany, approximately only 20-30% of eligible subjects underwent screening colonoscopy. Thus, alternative, less invasive and more acceptable screening options are desirable. In this dissertation, a focus was set on fecal immunochemical tests (FITs), which have generally good performance in detecting CRC. Detection of AAs remains very limited with a single application, though, making repeated screening advisable. Still, a fraction of AAs will be missed even with repeated FIT screening. Thus, additional tests or combinations of tests are warranted to enhance performance of FIT screening. Many studies investigated combined performance of FIT and other stool or blood tests. However, only few markers appear promising in combination with FIT, mainly DNA- and RNA-based markers, as opposed to so-far investigated stool proteins (other than hemoglobin) and blood markers. Most marker combinations, however, were not analyzed in screening settings, using adapted and externally validated cutoffs of both, FIT and the secondary marker to achieve specificities comparable to that of FIT alone.

In my meta-analysis, I quantified the sensitivities of FIT for distal and proximal colorectal neoplasms and found that FIT was consistently more sensitive for distal neoplasms. Differences were much larger for AAs as compared to CRCs. The potential gain by conduction of FS in addition to FIT is thus somewhat smaller than one would expect when sensitivities of FIT were identical for the entire colon and rectum. Expected overall sensitivities and specificities of FIT combined with FS for any AN, assuming colonoscopy referral due to any distal neoplasm was 75% at a specificity of 92% in the modeling approach using published data and 78% at a specificity of 94% in the modeling approach using original BliTz study data.

This dissertation indicates that a combination of a single FIT with a once-only flexible sigmoidoscopy (FS) may be a highly effective screening modality in terms of sensitivity and numbers needed to refer to colonoscopy per detected relevant finding compared to sole colonoscopy screening or individual testing with FIT or FS. These screening modalities complement each other due to the different mechanisms of detecting neoplasms (occult blood *versus* direct visualization). However, attention needs to be paid to several aspects when combining FIT and FS: To both tests, different positivity criteria can be applied which result

in a trade-off between higher sensitivities or fewer colonoscopies at the expense of a higher proportion of missed (FIT-negative, FS-unreachable) neoplasms. My study results indicate that the following procedure might achieve high detection rates despite comparably low colonoscopy referral rates: Initially, a FIT should be conducted, using a low positivity threshold to detect the majority of CRCs and a significant proportion of AAs. In FIT-negatives, a single FS should be conducted, and any adenoma or polyp detected should be removed.

My results and recommendations are in part based on my meta-analysis of published studies of which original data were not available and in part based on data from a very large CRC screening study from Southern Germany. Validation in further, large CRC screening populations also from other countries would be advisable to verify the findings. Such studies could also compare screening effectiveness in terms of CRC incidence and mortality when using different screening modalities and when compared to no screening. One study randomized subjects to a once-only FS with and without additional FIT. Its results indicate that a combination of FIT an FS might outperform testing with FS only. Investigations of CRC incidence and mortality comparing the different screening strategies combining FIT and FS proposed in this dissertation and also a comparison to other established CRC screening strategies are warranted. Such investigations should also consider cost-effectiveness of the different strategies. Offering different combined FS and FIT-based CRC screening strategies might contribute to higher screening participation rates if the advantages and disadvantages compared to screening colonoscopy and other screening tests are transparently communicated.