**Original-Titel:**

**Variability in adenoma detection rate in control groups of randomized colonoscopy trials: a systematic review and meta-analysis**

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## Aritificial intelligence and the push for small adenomas – all we need ?

Artificial Intelligence (AI) has been enthusiastically welcomed by the endoscopic community. However, most of the many potential applications have remained in the in vitro environment: That means that AI software has been developed and tested on images or videos only. However, polyp detection software by various companies has entered the field of clinical application and has been studied extensively in randomized trials. At the time of writing of this editorial, 19 such randomized trials are available as full publications1-19. They all show a more or less significant increase in detection of small adenomas. Since this seems to be difficult to understand, the same results are summarized over and over again in no less than 16 meta analyses 20-35 plus a protocol for another one36, plus, of course, a meta analysis of some of these meta analyses 37.

Is the paper appearing in this issue of the journal using the Medronic AI system 38 (ref) just another randomized trial ? The authors stress in the abstract that the topic „has had limited clinical evaluation“ which may not be entirely true (see above). The present study is distinct from most other randomized trials in several aspects: Here, the patient population was homogeneous, including only colonoscopies from a FIT-based screening programme. Furthermore, a cap, mostly Endocuff vision, was used at the discretion of the endoscopist. Endocuff per se has been shown to increase polyp yield in again more than 20 meta analyses 39, and lately also in a FIT_based randomized screening colonoscopy study in this journal 40. Caps were used in about 70% of colonoscopies, and

we wish that this would have been standardized. Finally, polyp and not adenoma detection rate was used as the main outcome parameter in contrast to almost all other studies.

The results show that polyp detection rate was slightly higher in the AI group at 85.7% compared with the control group at 79.7% (p=0.05). So basically, almost everybody had a polyp and more than 2/3 had an adenoma. No difference in adenoma detection rate (ADR) was found, but the level was already high in the control group. In other FIT-based screening programmes, ADR was as high as in this study´s control group in the Netherlands 41 and lower in studies from other countries, namely 55% in Spain 42, 51% in Sweden , and 41% in Italy 40. In primary screening colonoscopy, ADR is naturally lower, since not preselected by a stool test: In the recently published NordICC trial ADR was 31% 43, similar to the German screening colonoscopy setting 44. A recent review looked into ADR differences in the control groups in randomized trials and found generally a very wide variation. The overall mean value of 37.5% was however inceased by a factor of 1.6 within FIT-based screening programmes 45.

Case number calculation in the present study reads a bit strange („this study was powered to detect a 10% increase in polyp detection, from a detect rate of 20% in the control group up to 30% in the CADe group“), since in reality, polyp rate was almost 80% in the control group. Also, higher adenoma and polyp detection rates have been published in FIT-based screening colonoscopy programmes as outlined above. So, in essence, the study could have been underpowered, and with larger case numbers, an ADR increase from 65% to 71% could have been significant (if relevant is another question). Interestingly enough, numerical differences in adenomas were in the group < 5 mm (from 765 to 846) but also in the group > 1 cm (from 94 to 120 polyps), in some contradiction to most previous studies only showing small polyps to be found more frequently by AI, but this may be coincidental.

So, what can we conclude about clinical relevance of AI increasing ADR ? The first question is, do we see an upper limit of ADR which cannot be substantially improved any more by AI or other means – and therefore, may this study have reached the possible ADR ceiling. Looking at the RCTs mentioned above, the relative increase in ADR was dependent on the basic ADR level in the control group in most of the papers: Relative ADR increases were around 50% in low ADR papers 15, 18, about 30% in trials with ADR levels between 20-30% 11, 17, and 20-25% in studies with basic ADRE levels of 30-45% 8, 10, 14, such as in FIT-based screening programmes 2. This is somewhat logical - that there is less room for improvement in high ADR performers. We are confident that this will be the topic of another meta analysis soon. Tandem studies in AI showed an even greater effect on the adenoma

miss rate, but it is well known that tandem trials yield better results than comparative randomized studies 46.

The second question is, of course, the ultimate clinical relevance of increasing ADR from high to even higher levels. We know that ADR correlates with interval cancer rate, i.e. higher ADR prevents colorectal cancer better. However, we still do not know whether we have a cut-off ADR level, above which there is no or not much further improvement in cancer prevention. This was indirectly suggested by the Polish and Austrian follow-up studies 47, 48, which primarily took a cut-off level of 20% for their data analyses. In contrast, the Californian group suggested a linear correlation in their studies 49, 50. Their recent publication however includes figures which somehow contradict the conclusions 50. It appears logical, that if more than 2/3 of scoped persons have a (mostly small/very small) adenoma, then the risk factor ADR may of be less importance and finding more and more small adenomas may not be the key to success.

The third question is which adenomas should we chase and what else needs to be done. The relevance of small adenomas has been doubted by many database analyses in the last 10 years which correlated patients´ prognosis with the stage of adenomas found and removed during colonoscopy, again confirmed in a large review at the end of last year 51. Another recent meta analysis summarized the evidence of 12 such studies 52; The authors uniformly showed no relevant disadvantage with regards to colorectal cancer development for persons with small adenomas only, as compared to the normal population or people with a normal colonoscopy. The worrisome findingof all these studies  however is that the colorectal cancer incidence was 4fold higher when patients had advanced adenomas which were obviuously removed: Should these patients not benefit much more from colonoscopy and polypectomy and perhaps brought back to the normal risk level ? So, we presume, that there is more to colonoscopy quality and cancer prevention than just finding more and more small adenomas. We know that resection can be incomplete with sometimes worrisome rates 53-55, and so may be adherence to follow-up: Mostly, patients with small adenomas tend to be oversurveilled, those with advanced lesions undersurveilled 56-58 (and perhaps primarily underresected) . May we have the wrong focus here staring at ADR all the time ?

Finally, randomized trials, as high evidence they may provide, also may have shortcomings; the focus of a study and the willingness to produce good results and to achieve a better publication may increase the examiners awareness and attention in both groups (Hawthorne effect), but perhaps more in the study group, here for AI. On the other hand, there are recent sobering reports about what happens if AI systems are incorporated into a colonoscopy programme: Papers have shown that

ADR did not increase in an US center 59, or even decreased in an Israeli hospital 60, perhaps due to shorter withdrawal times. The group from Würzburg showed by eyetracking that trainees focus their eyes in the middle of the picture when using AI, while without AI, they tended to look around more 61. This phenomenon is known from radiology and called „deskilling“. This may not be the intention of AI, which – as we can conclude – is still dependent on the examiners ability to maneuver the scope adequatly and also to pay attention. If AI is expected to do the job, attention may be less

What do we need ? Studies should look at more relevant outcomes than just whether we find more small polyps (we already have abundant evidence that this is the case). Authors and editors should refrain from writing and accepting more and more meta analyses about AI polyp detection. And there are also more challenging applications to be studied, starting with tissue diagnosis (and histology replacement which may face quite a few legal and credentialing hurdles), but also performance, interpretation, documentation, risk stratification and follow-up of colonoscopies and patients with more advanced polyps, all parameters which have to be documented before, during and after colonoscopy. If some of this documentation paperwork is taken off our shoulders, we could perhaps better focus on good patient care and finally als on good clinical research.

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