Translation of DNA methylation markers for the early detection of renal cell cancer

IMPACT PARAGRAPH

In 2020, approximately 430.000 new cases of kidney cancer were reported globally, representing 2.2% of all cancers diagnosed[1]. In that same year, an estimated 180.000 deaths could be attributed to kidney cancer[1,2]. Renal cell carcinoma (RCC) is the most prevalent type of kidney cancer, responsible for 90-95% of all cases, and the incidence rates have been rising with 2% per year over the past two decades[2,3]. The 5-year survival rate of RCC confined to the kidney is 93%, whereas the 5-year survival of distant metastasized RCC is decreased to 13%[4]. Globally, 3.3 million disability-adjusted life-years were estimated for RCC in 2017, and the disease burden has not decreased over the past 30 years despite advancements in RCC management[5,6]. With the increasing use of imaging techniques, a substantial proportion of patients are diagnosed after a coincidental finding during an unrelated procedure[7,8]. The rising incidence, partly caused by the increasing amount of incidental findings, together with the aging population will continue to increase both disease and economic burden because of RCC.

The increasing amount of incidentally diagnosed small renal masses (SRMs), and the fact that only 50-70% of these SRMs are correctly being diagnosed as benign or malignant based on medical imaging, goes hand-in-hand with overtreatment of many patients[2,4,7,8]. Whenever the nature of an SRM is uncertain, partial or radical nephrectomy can be decided upon. Patients will undergo burdensome surgeries to remove (part of) a kidney, never without risks of complications, which after pathological evaluation turn out to have been unnecessary in 25% of cases[9]. In addition, patients experience current diagnostic procedures like computed tomography (CT) scans and magnetic resonance imaging (MRI) scans as unpleasant because of scan duration, loud noise and space- and motion restrictions[10,11]. Next to that, these imaging procedures are considered time-consuming, not only because of the duration of the scan itself, but also because patients have to travel to and from the hospital[10]. From a hospital- and societal burden perspective, imaging techniques are also burdensome in terms of costs, time, effort and the need for specialized staff. Taken together, this emphasizes the importance of improving the current regime in accurately diagnosing RCC in early stages. To limit and potentially substitute part of burdening diagnostic imaging procedures, more accurately diagnose SRMs and avoid overtreatment, studies have been aiming to improve RCC diagnostics by focusing on non-invasive molecular markers in liquid biopsies. These patient-friendly diagnostic biomarkers for RCC could reduce both health- and economic burden not only by directly replacing costly and unpleasant imaging procedures, but also by avoiding unnecessary surgeries and subsequent medical follow-up.

Despite the great interest and research invested in molecular markers to replace invasive procedures, only <1% of all published biomarkers have reached clinical care[12,13]. This is in line with the fact that a large proportion of research investments being avoidably

wasted at this moment[14]. Unfortunately, the same holds true for DNA methylation biomarkers specifically, illustrated by the fact that not a single DNA methylation biomarker for diagnosing RCC has reached clinical care.

After initial publication, the vast majority of biomarkers never reach the stage of validation. In this thesis, we have addressed several reasons for the lack of success and validation and illustrated the effect of assay type, assay design, sample type, sample selection and control selection on biomarker development in the individual chapters of this thesis. In addition, we discussed to adequately address all these problems when performing a biomarker study. As argued in **Chapter 7**, validation studies are considered less innovative as compared to identification of novel biomarkers, and therefore also less of interest to scientific journals and funding agencies, leading to publication bias and an imbalance in funding streams[15]. Changing this scientific mentality is a shared responsibility of the academic community, including researchers, peer reviewers, journals, editors, universities and funding organizations. Filling knowledge gaps, rather than creating even more of them needs to be supported, facilitated and enforced by all parties. Accordingly, reducing research waste starts with many considerations upfront, rather than merely in the lab.

Suggestions provided in this thesis strive towards more efficient use of biomarker research funding, thereby not only reducing research waste, but also increasing the chance of developing clinically useful biomarkers for the accurate and early diagnosis of RCC. In that way, the results and perspectives from this thesis have both scientific and economic impact, as changing the biomarker research mentality will encourage decent and reproducible research, thereby facilitating validation of biomarkers, and subsequently allowing clinical utility of these biomarkers. The clinical applicability of these biomarkers will in turn lead to a reduction in health- and economic burden, by replacing and sparing imaging procedures, surgeries and medical follow-up.

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