Diagnostic Forum 2013

From identification to large-scale clinical implementation of multiple biomarkers in prostate cancer

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Karolinska Cancer Risk Prediction Center (CRiSP) is developing individual cancer prediction and prevention

CRiSP (www.crispcenter.org) Key Characteristics

Objective	**Individual cancer risk prediction and prevention**
Method	**Cross-disciplinary, translational research**
Funding	**MSEK 200+ funding from Swedish Research Council, Märit and Hans Rausing and Stockholm County Council**
Focus	**Breast and prostate cancer**

Stockholms läns landsting

Märit and Hans Rausing initiative against breast cancer

Vetenskapsrådet

We have access to the world's best characterized patient material

Examples of patient material available

	Cancer	Study type	Recruited	Recruitment per week	Data collected	
					Phenotype	Bio-samples
Karolinska Mammography Project for Risk Prediction of Breast Cancer : Karma	Breast	Prospective	**65,000**	**1,000**	◆	◆
Stora prostata-cancerstudien: STHLM 0	Prostate	Register	**380,000**	**500**	◆	NA
Stora prostata-cancerstudien: STHLM 2	Prostate	Prospective	**26,000**	**Completed**	◆	◆
STHLM 3 Stora studien inom prostatacancer	Prostate	Prospective	**10,000**	**2,000**	◆	◆

Our cohorts are designed for research

Example of cohorts available

Key features	Karolinska Mammography Project for Risk Prediction of Breast Cancer : Karma	Primary Prevention of Prostate Cancer STHLM 2	STHLM 3 Stora studien inom prostatacancer
Broad consent	◆	◆	◆
Prospective cohort with high recruiting rates	◆	◆	◆
Near-real-time access to data and bio-specimens	◆	◆	◆
SNP genotyped	200k SNPs		118 SNPs
Continuously matched against national registers and option to match against hospital records	◆	◆	◆
Bio-samples handled in accordance to strict 30h protocol	◆	◆	◆
Front-end analyzis of key biomarkers			◆

Let’s talk about prostate cancer

The last 30 years have seen many improvements in prostate cancer treatments

- Prostate cancer is the most common cancer in the western world
- Lifetime risk 10-15%
- Billions have been spent on research the last 30 years
- 100+ potential markers for diagnostics available
- Significant improvements in treatment with robot assisted surgery and precision radiology

But current diagnostics with PSA has several issues disenabling it for screening purposes

- **PSA misses about 20% of severe cancers** and not possible to increase sensitivity. Lowered cut-off only led to increase number of biopsies but not increased number of cancers found
- **PSA leads to serious over-diagnosis**. 2 out of 3 diagnosed have no cancer
- **PSA cannot distinguish between indolent and aggressive cancers**

The U.S. Preventive Services Task Force gave PSA screening a grade of “D”. **This is a recommendation against PSA-based screening for men of any age**. (May 2012)

Other markers in addition to PSA are not widely used in clinical practice

Examples of other markers

PCA3	Urine mRNA marker
Beckman PHI	Combination of proPSA, total PSA and free PSA

Not widely used due to weak health economics

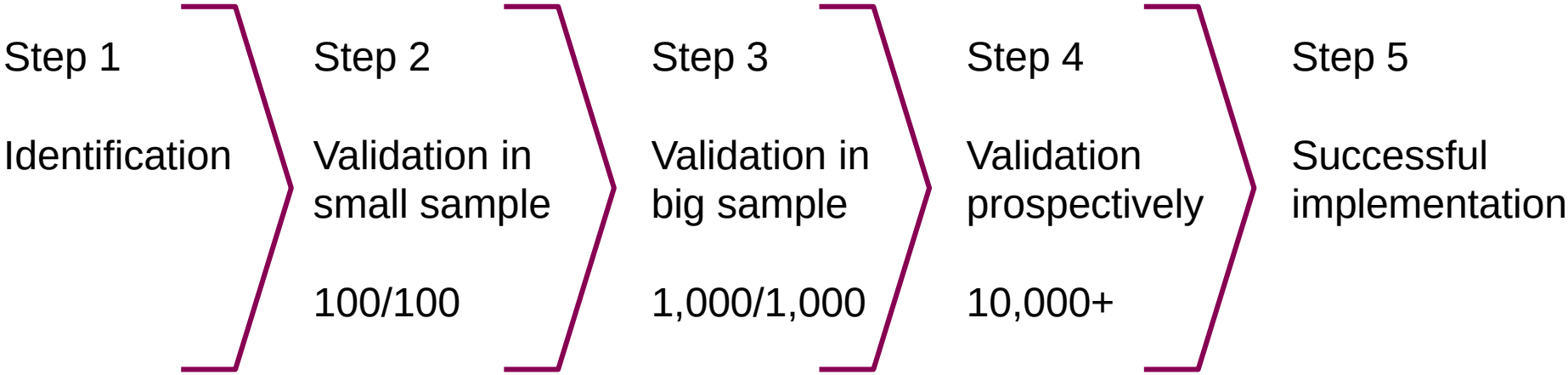
Still, there is a lot of activity in developing new improved markers, most hampered by access to comprehensive patient material

Examples of marker development initiatives in prostate cancer

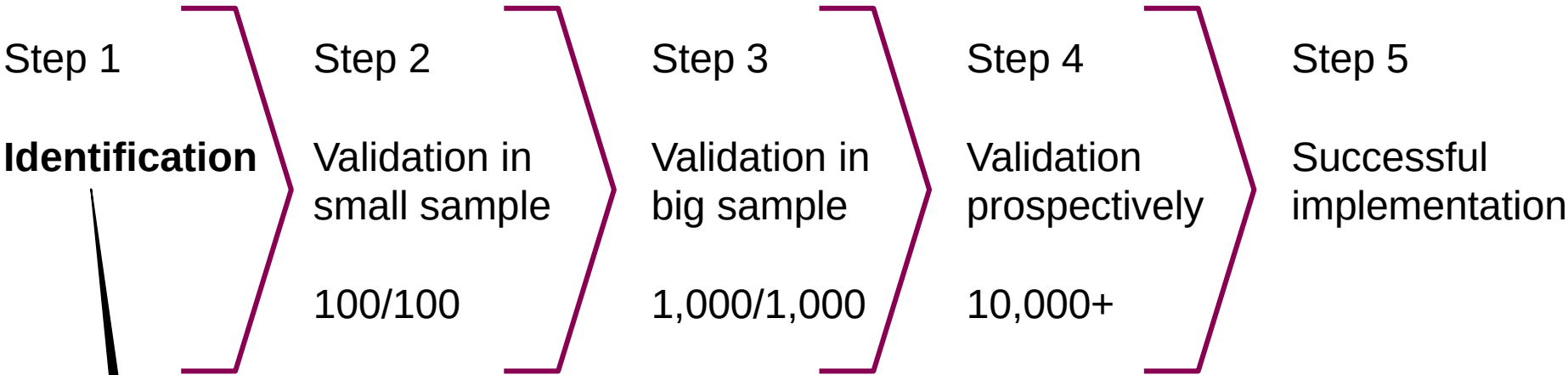
Ambrilia Biopharma Canada immuno PSP94 protein for prostate cancer dev, BioImagene Cupertino, CA IT Ki-67 prostate image analysis algorithm rsch, bioMerieux France protein Annexin 3 marker on Vidas, urine dev, Prostate Cancer FISH Detection, TMPRSS2, HGPIN-1, pre-malignant prostate cancer, urine dev, ChromoCure Reno, NV FISH CS200 Chromosomal Scanner rsch, Clarient U.S. FISH Prostate Gene Expression Profile service, IRIS International Chatsworth, CA immuno NADiA ProsVue dev, LabCorp Burlington, NC PCR Veridex's methylated GST-Pi, service, dev, MacroArray Tech Philadelphia, PA protein PCADM-2, prostate cancer dev, MacroArray Tech Philadelphia, PA protein, Health Discovery Corp Savannah, GA PCR four-gene prostate cancer test dev, Exosome Diagnostics New York, NY exosomes prostate cancer screen, RNA, urine dev, MacroArray Tech Philadelphia, PA immuno cell-phone sensor urine prostate cancer Dx dev, Metabolon RTP, NC protein sarcosine, prostate cancer progression dev, Miraculins Edmonton, AB immuno, PSP94 & vitronectin on Luminex system, urine dev, OncoMethylome Netherlands methyl hypermethylated GST-Pi gene service, dev, …

- **Typically limited value from each individual marker**
- **Typically tested in small cohorts (<500 individuals)**
- **Need large, well characterized cohorts/prospective studies to be validated**

Research toward successful clinical implementation of new bio-markers needs to follow a five step process



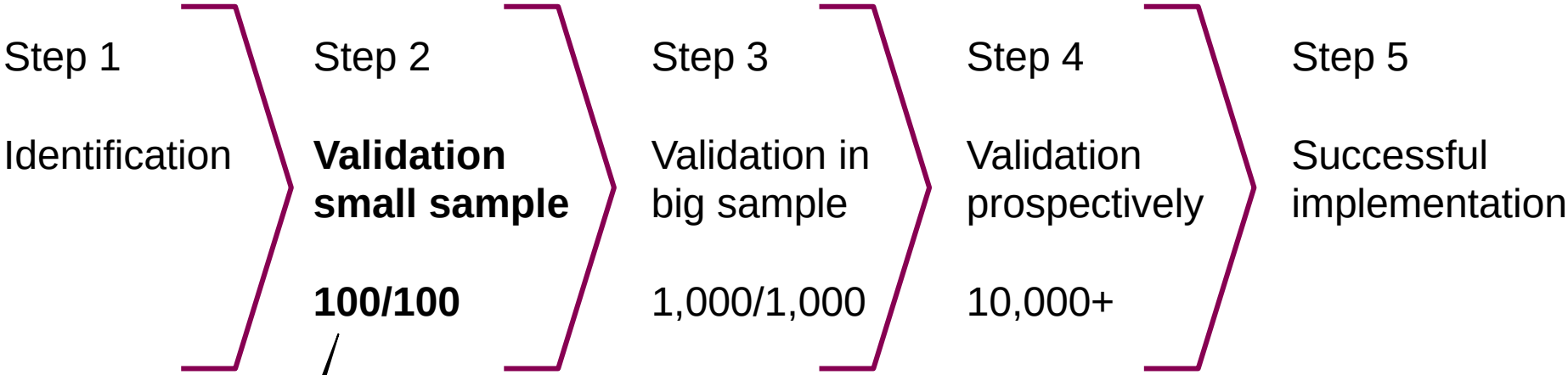
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Key Success Factors

- **Thorough literature search**
- **Strong Scientific Network**

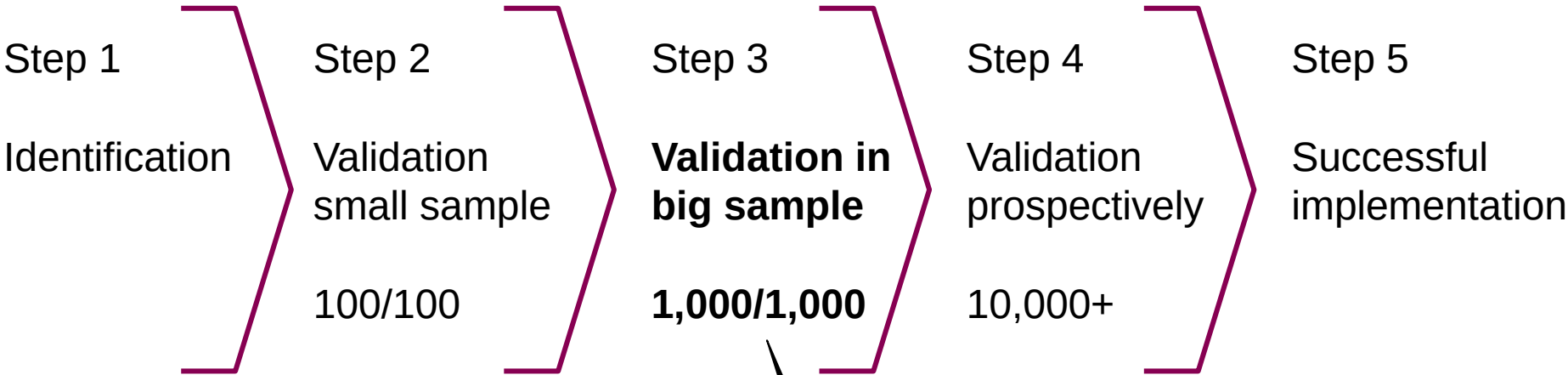
Research toward successful clinical implementation of new bio-markers needs to follow a five step process



Key Success Factors

- **Stringent sampling protocol, i.e. cases/controls sampled at same time, according to same protocol and matched against age, time of year, etc.**
- **Samples must be clinically well defined**

Research toward successful clinical implementation of new bio-markers needs to follow a five step process

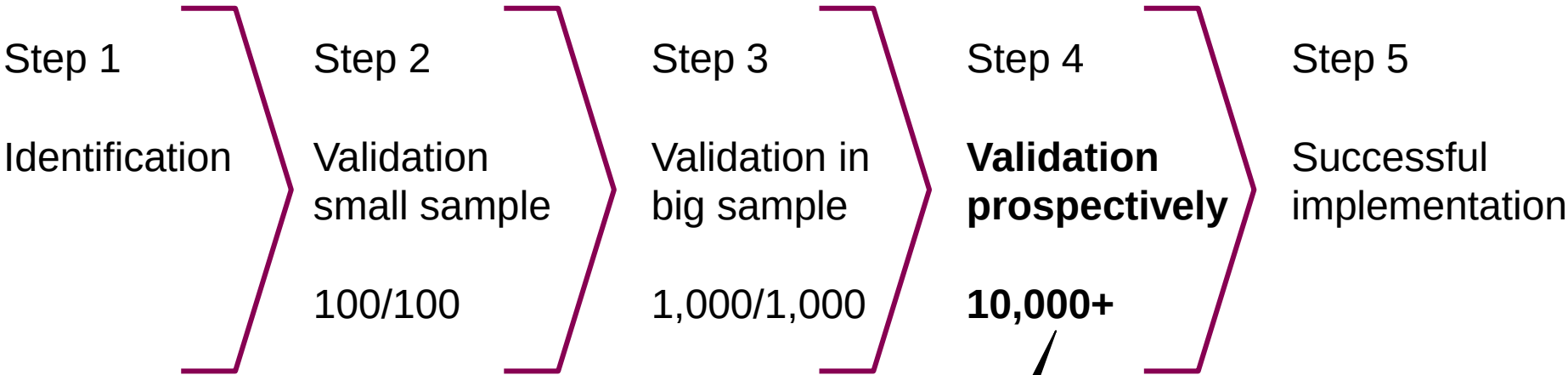


Key Success Factors

- **Stringent sampling protocol**
- **Samples must reflect clinical relevant situation**
- **Samples must be clinically extremely well defined**

Very different sample mix compared to step 2

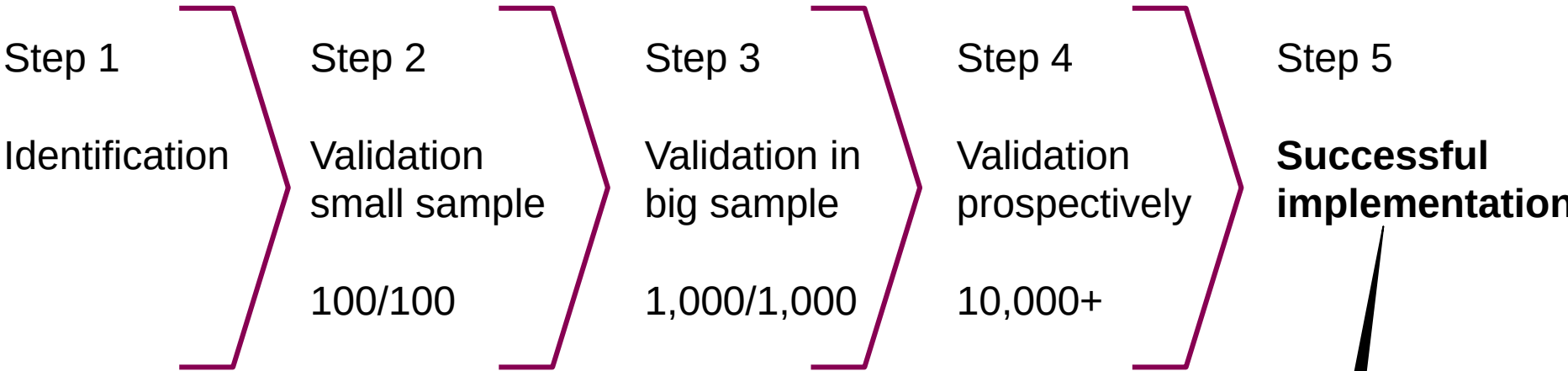
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Key Success Factors

- **Prospective setting with no testing bias**
- **Samples must reflect clinical relevant situation**

Research toward successful clinical implementation of new bio-markers needs to follow a five step process



Key Success Factors

- **Strong health economic case**
- **Strong clinical and scientific anchoring**
- **Up-front cooperation with health care provider, regulatory bodies and industry**

Case example – STHLM3

There is a de facto screening with PSA in Stockholm today

Common cancer

- Approximately 2,000 men are diagnosed yearly in Stockholm with prostate cancer

De facto screening in Stockholm

- Approximately 130,000 PSA test were taken 2010 (~25% follow-ups)
- Increasing trend, 15% yearly increase the last 4 years
- 60-70% of men aged 50-69 have been tested
- Approximately 7,000 biopsies performed 2011

Unstructured

- Many men take PSA as part of health screening (mostly without symptoms)
- Many takes PSA without knowing what it is
- >50% of tested above 65 years

STHLM3 aims to reduce unnecessary biopsies while keeping the same sensitivity as PSA to find aggressive cancers

To increase the specificity of a combined prostate cancer test compared to the PSA test without decreasing the sensitivity of aggressive prostate cancers

STHLM3 will significantly improve diagnostics of prostate cancer by combining 100+ markers

Improved diagnostics based on combination of 100+ markers

- Enables screening
- Enables exclusion of 50%
- Differentiate severe from non-severe tumors
- Significant reduction in un-necessary biopsies
- Reduce anxiety – improved quality of life

STHLM3 status and next step

- 100+ biomarkers and SNPs identified and validated in small and big validation cohorts
- Prospective validation in STHLM3 in 2013-2014
- Continuous screening and evaluation of additional markers

We are actively looking for additional biomarkers

Take home message – sample is king

1. Multiple markers can be tested cost efficiently in parallel
2. Systematic screening, validation and testing is necessary to find and test multiple markers
3. Clinically well defined samples are needed
4. Prospective testing is necessary to avoid bias

