

# A Multi-parametric, Nuclear Magnetic Spectroscopy based, accurate assessment of renal filtration by combining creatinine, myo-inositol, valine, and cystatin-c with age and gender

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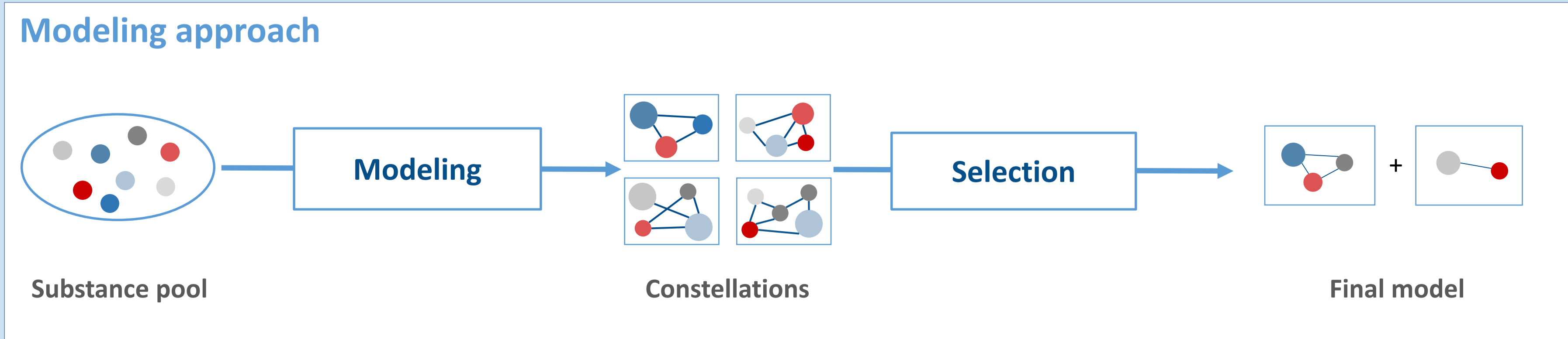
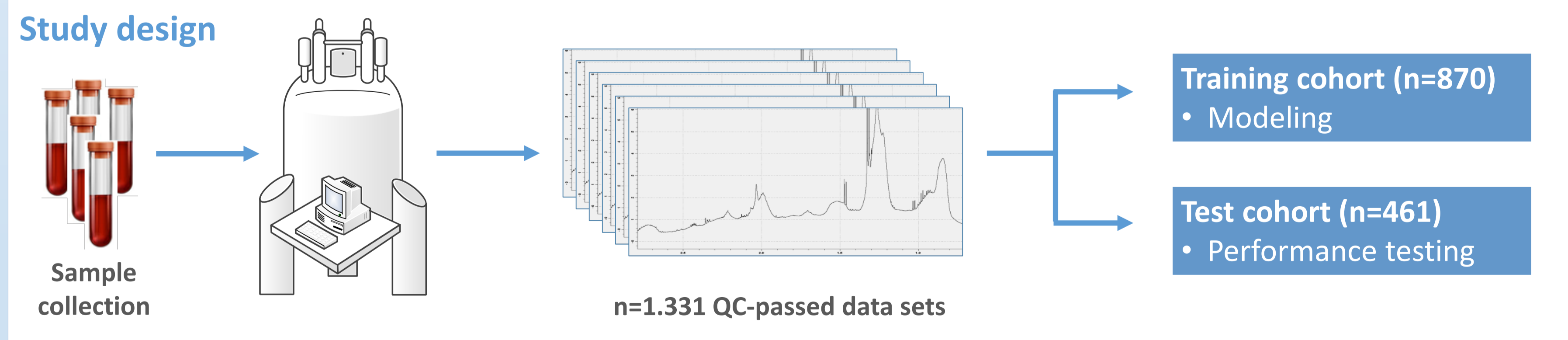
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## BACKGROUND

Multiple-biomarker panels are increasingly utilized to overcome limitations of classical single biomarker assays. Glomerular filtration rate (GFR) estimation by single biomarker, creatinine or cystatin-c currently suffers from accuracy across the GFR range. We propose nuclear magnetic resonance spectroscopy (NMR) as a diagnostic platform capable of numerous metabolite measurement as a method to improve the current glomerular filtration rate (GFR) estimation method.

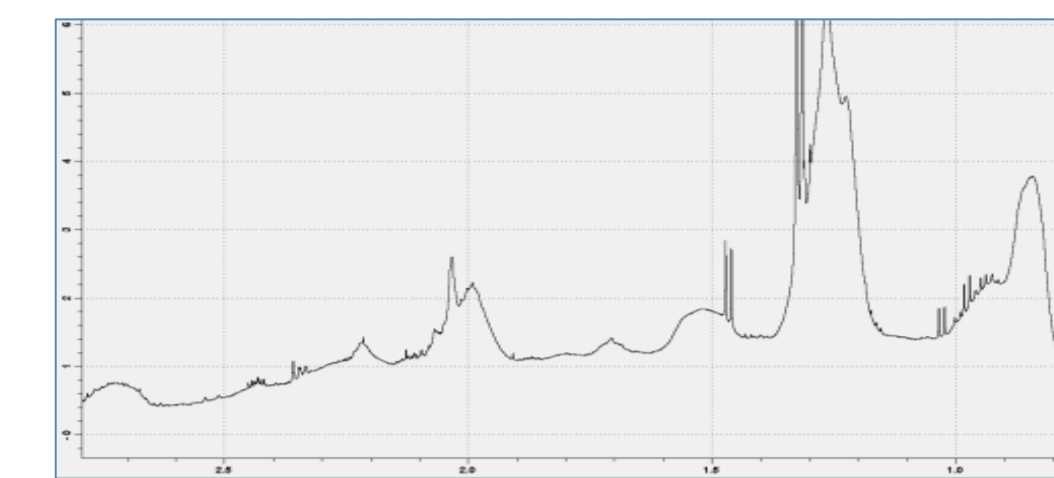
## GFR<sub>NMR</sub> / METHODS

We combined NMR metabolite measurement with artificial intelligence to identify multiple biomarkers associated with glomerular filtration rate (GFR) and chronic kidney disease associated metabolic dysfunction. Using NMR, we identified a pool of eight metabolites associated with GFR. Together with cystatin-c, age and sex, these metabolites were subjected to exhaustive machine-learning using piece-wise linear regression for accurate GFR prediction in (n=870) training samples using radiotracer measured GFR (mGFR) as a reference. The final constellation was validated in (n=461) independent samples in an international multi-center sample set.



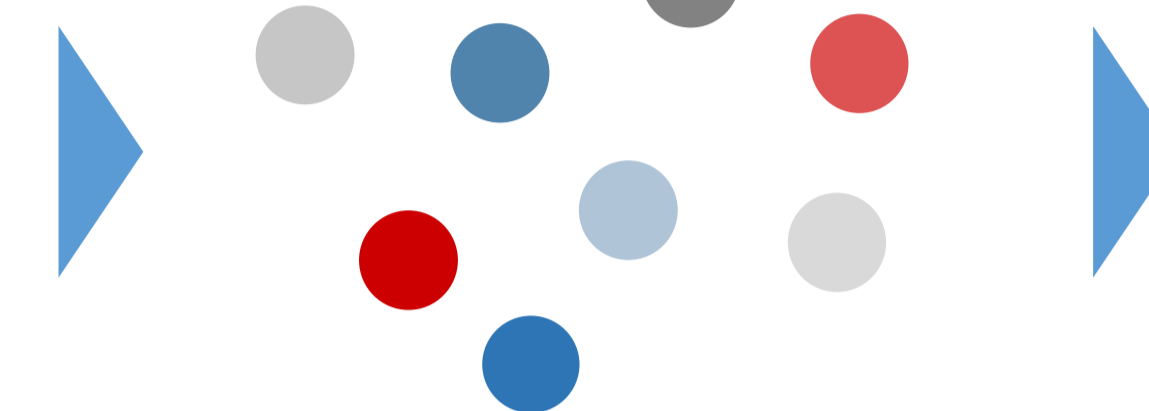
## RESULTS

### From spectrum to diagnosis: Model selection GFR<sub>NMR</sub>

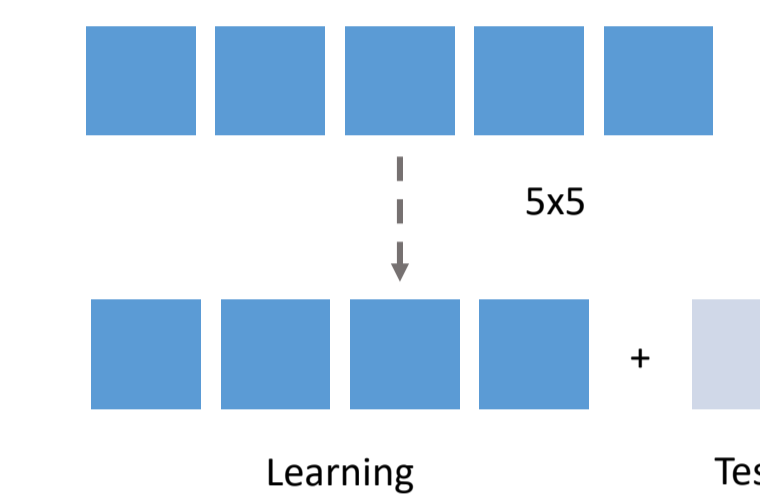


Automatic processing & quality control → Adaptive binning → Metabolite Identification

Identification of NMR signals that significantly correlate with mGFR; curve-fitting was applied for robust quantification

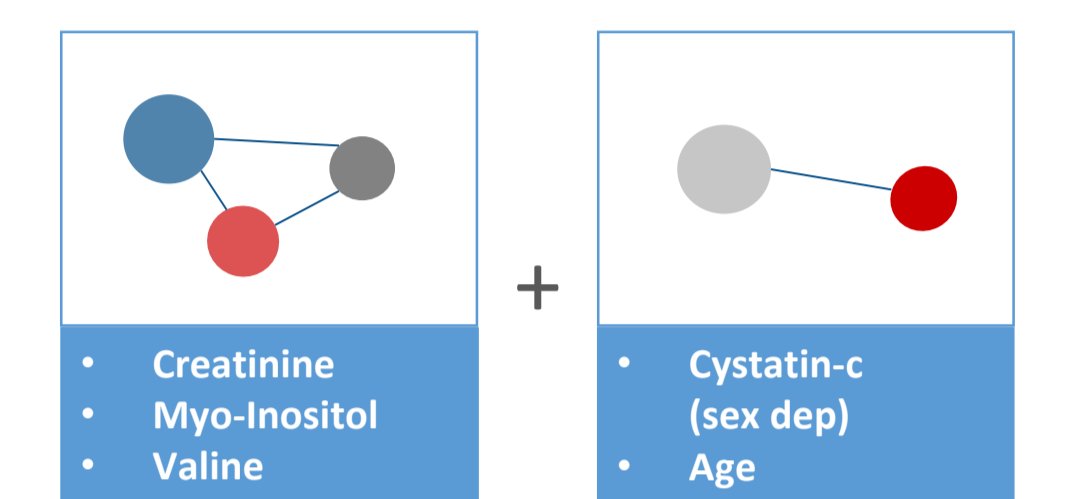


### Training Cohort



487,408 models were tested for concordance with mGFR (five-times repeated 5x cross-validation); the most suitable model was selected via a multi-stage selection process

### Final model: GFR<sub>NMR</sub>



Sex-dependency was introduced for cystatin-c via piece-wise linear regression and age was added for further improvement

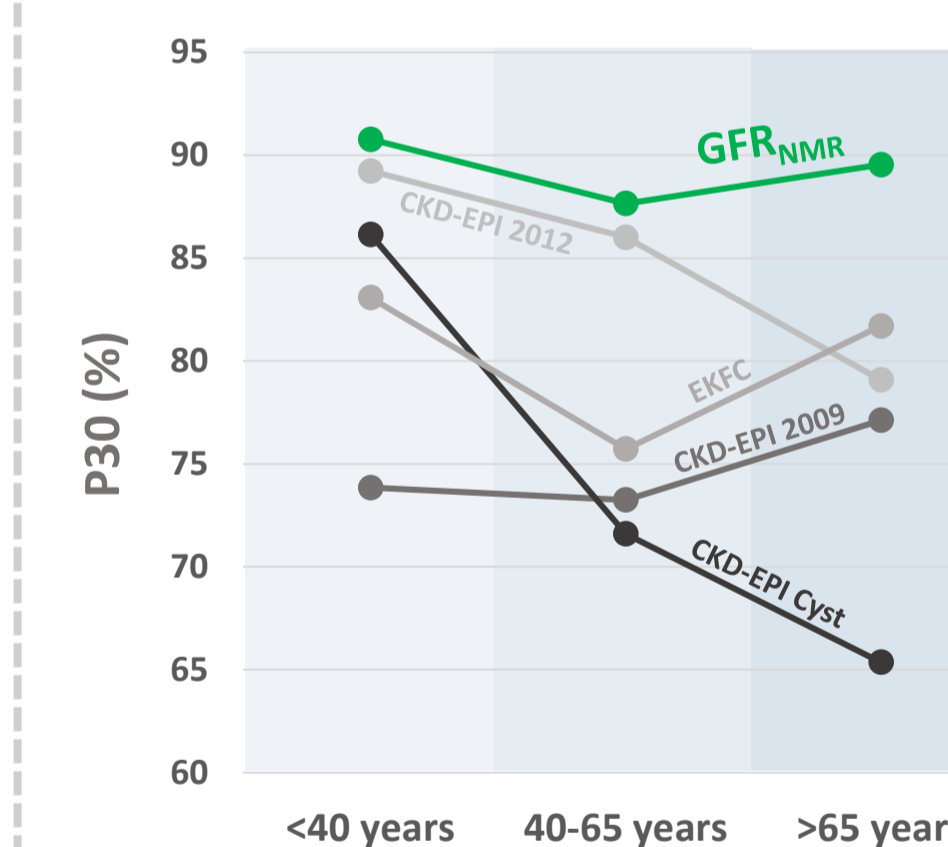
## Performance of the final model was assessed in the independent test cohort (n=461)

### Overall performance of GFR<sub>NMR</sub> was superior to current eGFR formulas

Formula	Overall test cohort		
	P30	P20	P15
<b>GFR<sub>NMR</sub></b>	<b>88.72</b>	<b>72.23</b>	<b>57.27</b>
CKD-EPI 2012	84.16*	65.08*	55.1
CKD-EPI 2009	74.62**	58.13**	47.72*
CKD-EPI Cyst	71.58**	50.98**	41.00**
EKFC	78.74**	60.09**	47.94*

Significance level adj. p-value (McNemar test), comparison GFR<sub>NMR</sub>: \* < 0.003; \*\* < 0.0001

### GFR<sub>NMR</sub> showed constant performance over the full range of age



Formula	Age < 40 years		Age 40-65 years		Age > 65 years	
	P30	RMSE	P30	RMSE	P30	RMSE
<b>GFR<sub>NMR</sub></b>	<b>90.77</b>	<b>19.03</b>	<b>87.65</b>	<b>14.03</b>	<b>89.54</b>	<b>11.26</b>
CKD-EPI 2012	89.23	18.02	86.01	15.10	79.08	13.14
CKD-EPI 2009	73.85	22.59	73.25	19.26	77.12	14.15
CKD-EPI Cyst	86.15	20.91	71.60	18.82	65.36	15.80
EKFC	83.08	21.47	75.72	18.37	81.70	13.51

## CONCLUSIONS

Radiotracer mGFR is the gold standard but limited by availability. For routine clinical use, creatinine and cystatin-c based formulas are common practice but have accuracy limitations.

A metabolomics-based GFR<sub>NMR</sub> was superior to both the current CKD-EPI formulas and the newly developed EKFC formula for GFR estimation.

## CONTACT DETAILS

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