# PARRS RISK SCORE

A Renal Risk Score Development By An Artificial Neural Network

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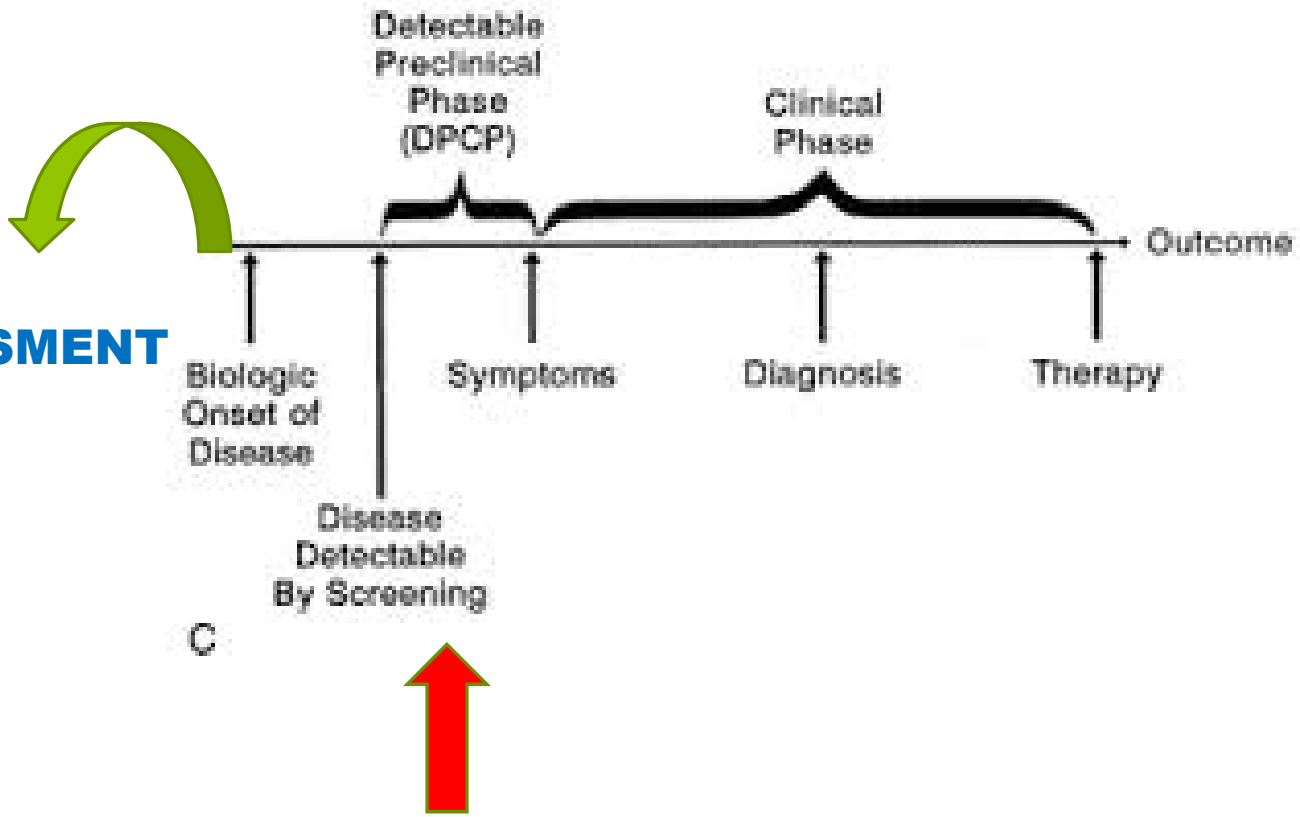
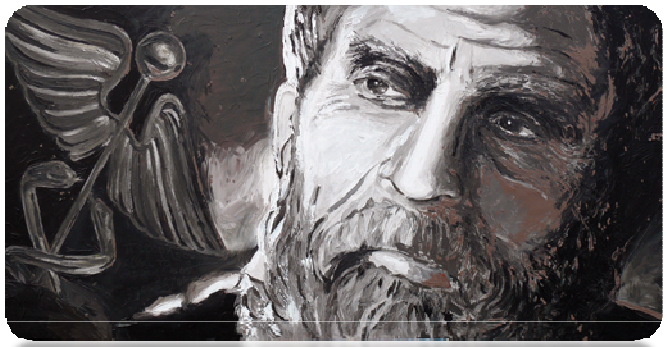
# Why Screening and Risk Assessment?

**Even Earlier:**
**RISK ASSESSMENT**



# Footsteps in the history of medicine

Increased health risk due to obesity and alcohol has been mentioned in ancient writings of **Hippocratus** (370 BC).



**Galen** (The father of experimental medicine, 130-210 AD) introduced the theory of Humorism and had interesting comments on the polycystic kidney disease and about the circulation physiology and risk factors.

Rhazes (the Galen of Islam, 865-925 AD)described risk factors for renal stone formation and prescribed herbals to avoid recurrence. He noted differential diagnosis for anuria and hematuria by combination of Clinical markers.

Avicenna (The King of Medicine, 980-1037 AD) predicted renal outcomes by uroscopy findings and added patients' characteristics (age, gender, Obesity, …) into account for the stone risk assessment. He also described about 20 CV risk factors and developed Clinical Sphygmology.

# Pre-Modern Approaches
# (Bad Drivers)

Regress
Mitch W
metho
Lancet;

simple
failure.

Proteinu
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Isseki et

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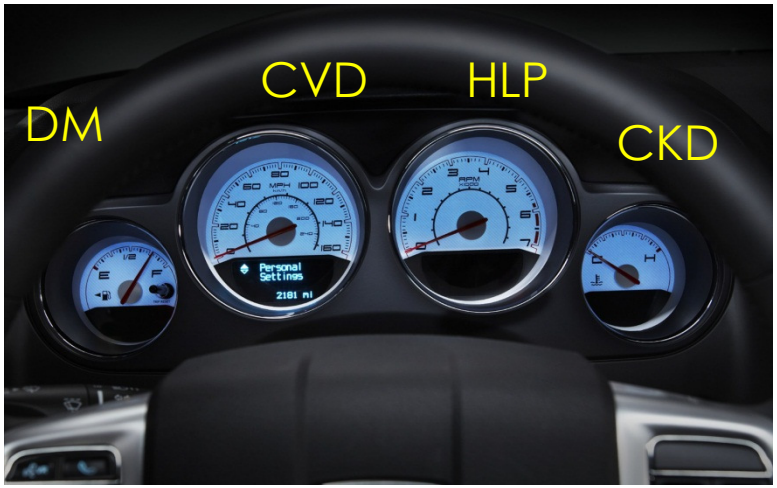
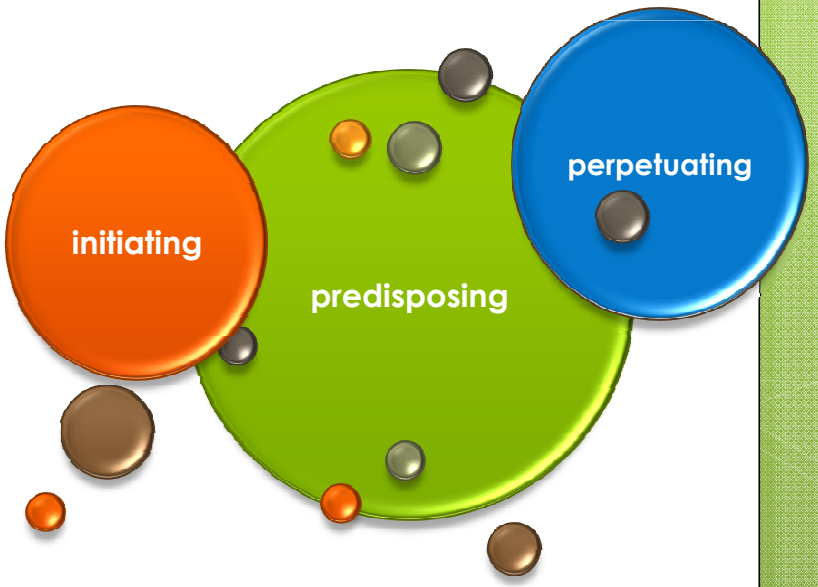
Microal

some cases

# Modern Approach
# (Bad Engine)

- physician-centric and physician-dominated
- Sub-spacialties
- Decision Check points (e.g. HTN, DM, HLP,…)



# Post-modern Era (Scoring)

patient-centric, on science and technology-dominated. It relies, on evidence, on genomics, bionics, proteomics

personalized, regenerative, on simulation and digital medicine ….

Consider Heterogeneitis


I'M WORRIED THAT HEALTH CARE HAS BECOME TOO IMPERSONAL, DOC.
NONSENSE... JUST RELAX AND LIE BACK ON THE BAR CODE SCANNER.
Rob Rogers / Pittsburgh Post-Gazette

# Scoring Systems

- **Multivariate Regression Analysis**
- **Cox-Proportional Hazard Analysis**
- **Decision-tree Simulations**
- **Bayesian Modeling**

*There is an urgent need for a simple method of risk assessment for all patients with CKD (Taal- KI, 2008)*

# NHANES and ARIC studies

Risk factors for CKD (GFR<60 ml/min)

Age
Gender
HTN
Anemia
DM
PVD
CVD history
CHF
Proteinuria

Cross-Sectional:
8530

**TEST SET:**
ROC=0.88
PPV= 0.18
NPV=0.99
**VALIDATION SET:**
ROC=0.71

Cohort
14155

**TEST SET:**
ROC=0.69
PPV= 0.17

Bang et al, Arch Intern Med (2007);167: 374-381
Kshirsagar et al, Arch Intern Med (2008): 168: 2466-2473

Chien et al, Am J Med (2010); 123: 836-846

Age
Gender
BMI
HTN (DBP)
Uric Acid
Anemia
DM (+HbA1C)

Chnese Cohort:
5168

**TEST SET:**
ROC1=0.77
ROC2= 0.67

HipCox et al, BMC Fam Prac(2010); 11: 49

Added:
Ethnicity
SEC, NSAIDs
SLE
7 years Follow-up

UK >1.5 million
primary Care

**(MOD to SEV)-CKD**
**TEST SET :**
ROC=0.82
**Validation SET:**
ROC= 0.88

# PREVEND study

Risk factors for CKD (GFR<60 or 20% decline)

MDRD-eGFR
Age
Gender
Sys-HTN
Albuminuria
CRP

Population-based
6809
6.4 y. follow-up

**TEST SET:**
ROC=0.84
PPV= 0.28
NPV=0.98
**Only int. VALIDATION**
**Only white population**

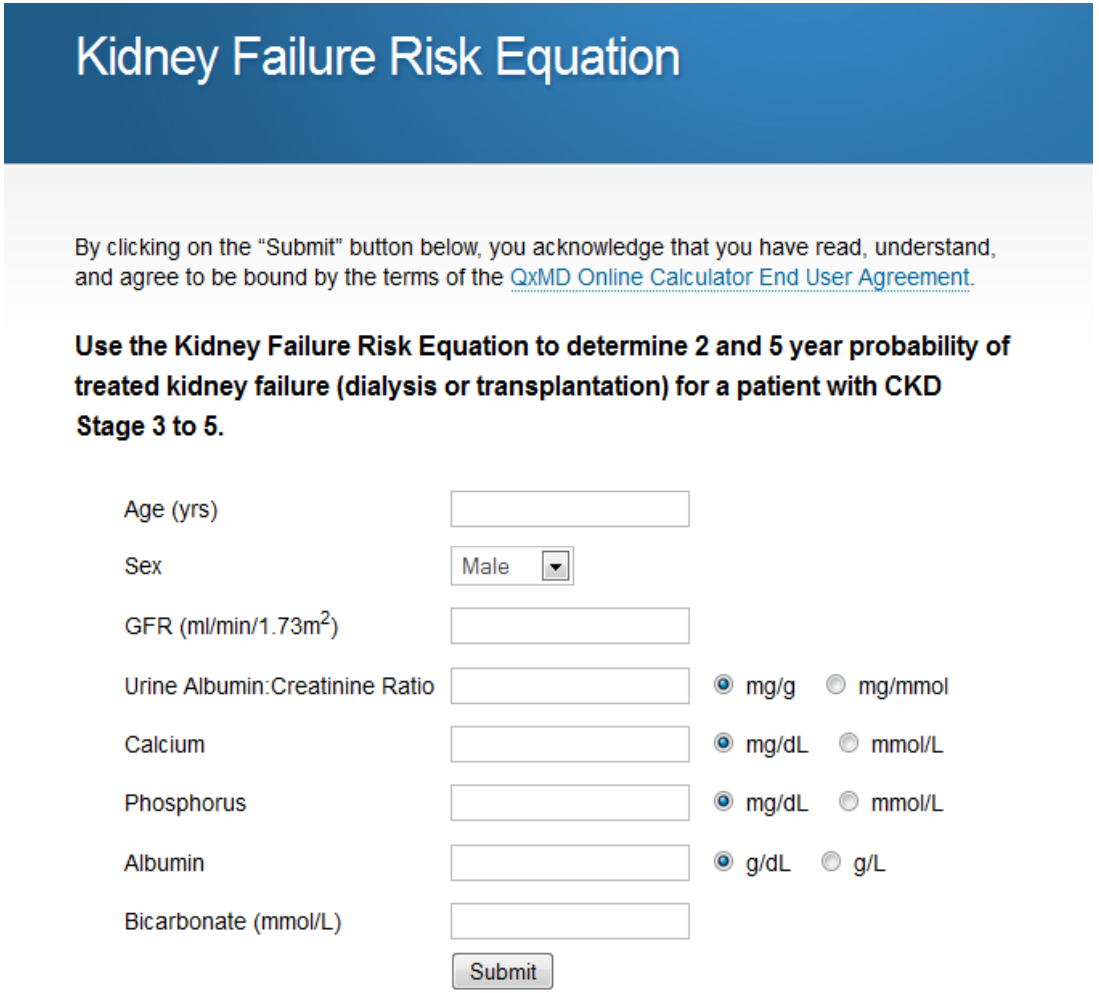
Halbesma et al, Clin J Am Soc Nephrol (2011); 6: 222

## QXMD-risk score

- REGISTRY for CKD stage 3-5
- 4942 pts
- Model included:

1. Age,
2. sex,
3. eGFR,
4. AlbU,
5. sCa, sP, sHCO3,
6. s-albumin

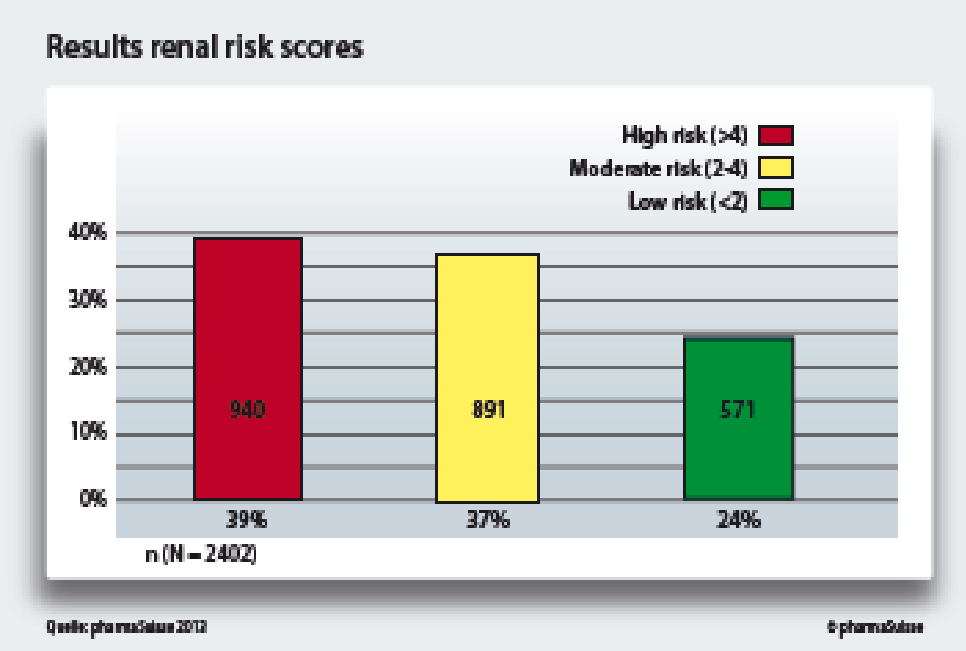
- C-Statistics=0.92
- Not include HTN, DM….
- Not exclude RF




Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305(15). DOI:10.001/jama.2011.451

# Have The Renal Risk Score Dream Come True?!

Astrid Czock et al/ 2013
2402 people screened in Switzerland by a Renal Risk Score including
AGE
SEX
Family History
Personal History
BP
ACR




NEPHRO
SWISS SOCIETY OF NEPHROLOGY

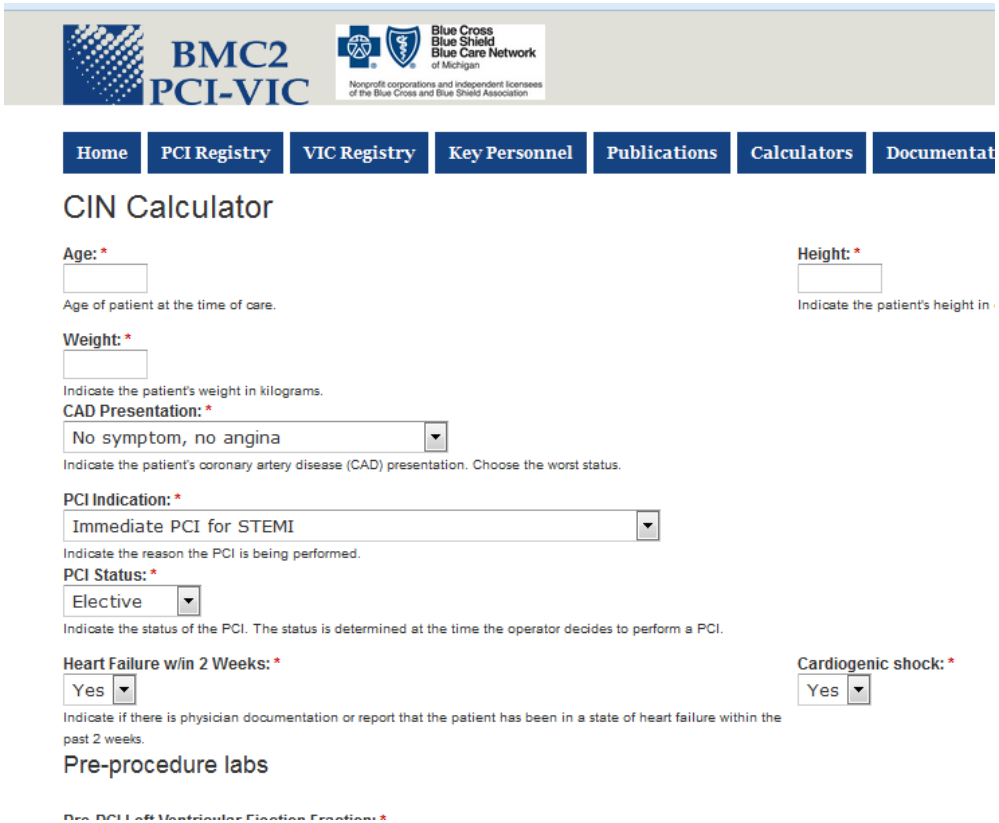
NOT FOLLOWED-UP, NOT VALIDATED !!!

# Contrast-induced Nephropathy (CIN) risk estimator

- 68573 PCI cases, Multicentre in Michigan 2010 to 2012
- Model included:

age, sex, race, creat, Hb, Trop, clinical, mediciations

- AUC=0.85 for contrat-induced nephropathy and AUC=0.87 for dialysis need
- Classified Risk levels
- Doubt in CIN diagnosis
- No follow-up
- Limited Clinical Use




**Hitinder, et al, JACC, Vol. 61, No. 22, 2013, 2242-8**

From: **Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality**

JAMA. 2014;():. doi:10.1001/jama.2014.6634

Risk of End-Stage Renal Disease by Change in Estimated Glomerular Filtration Rate (GFR) During a 2-Year Baseline Period, First Estimated GFR, and Subsequent Follow-up. Baseline risk is calculated for participants with 0% change in estimated GFR, estimated GFR of 50 mL/min/1.73 $m^2$, age of 60 years, male sex, nonblack race, systolic blood pressure of 130 mm Hg, total cholesterol level of 5 mmol/L, and without diabetes or a history of cardiovascular disease.

| First Estimated GFR During a 2-Year Baseline Period | Follow-up After Last Estimated GFR, y | Change in Estimated GFR During 2-Year Baseline Period, % | | | | | |
|---|---|---|---|---|---|---|---|
| | | -57 | -40 | -30 | -25 | -20 | 0 (Stable) |
| 20 | 1 | 63 | 31 | 19 | 15 | 11 | 3.9 |
| | 3 | 97 | 72 | 52 | 43 | 34 | 13 |
| | 5 | 100 | 94 | 80 | 71 | 60 | 26 |
| | 10 | 100 | 100 | 99 | 97 | 92 | 57 |
| 35 | 1 | 20 | 8.1 | 4.8 | 3.7 | 2.7 | 0.95 |
| | 3 | 54 | 25 | 16 | 12 | 9.2 | 3.3 |
| | 5 | 82 | 47 | 31 | 25 | 19 | 7.0 |
| | 10 | 99 | 83 | 64 | 55 | 44 | 18 |
| 50 | 1 | 5.0 | 1.9 | 1.1 | 0.86 | 0.63 | 0.23 |
| | 3 | 16 | 6.4 | 3.8 | 3.0 | 2.2 | 0.80 |
| | 5 | 32 | 14 | 8.1 | 6.4 | 4.7 | 1.7 |
| | 10 | 66 | 33 | 21 | 17 | 12 | 4.8 |
| 65 | 1 | 0.71 | 0.20 | 0.090 | 0.061 | 0.037 | 0.014 |
| | 3 | 3.9 | 1.1 | 0.49 | 0.34 | 0.21 | 0.079 |
| | 5 | 12 | 3.5 | 1.6 | 1.1 | 0.68 | 0.26 |
| | 10 | 37 | 12 | 5.5 | 3.9 | 2.4 | 0.90 |
| 80 | 1 | 0.45 | 0.12 | 0.054 | 0.038 | 0.023 | 0.0090 |
| | 3 | 2.5 | 0.70 | 0.31 | 0.21 | 0.13 | 0.050 |
| | 5 | 7.9 | 2.2 | 1.0 | 0.69 | 0.42 | 0.16 |
| | 10 | 25 | 7.7 | 3.4 | 2.4 | 1.5 | 0.58 |

Colors indicating absolute risk gradient, % (based on percentiles of the cells in the table):

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 100 | 73 | 43 | 20 | 12 | 5.2 | 3.1 | 1.1 | 0.62 | 0.16 | 0.01 |

## Clinical Application of "Renal Risk Scores":

# Where do we stand?

1. How popular they are in Clinical Practice?
2. Could we extrapolate evidences to our patients?
3. What happens if new markers will be introduced?
4. How can we deal with changing demographics?
5. Can we assess the net impact of our medication?
6. Are they applicable in different population?
7. Are these really early detectors?
8. How to mix with CV risk scores


*Identifying & understanding the new, advanced approaches in Nephrology for better renal health*

# ANN characteristics

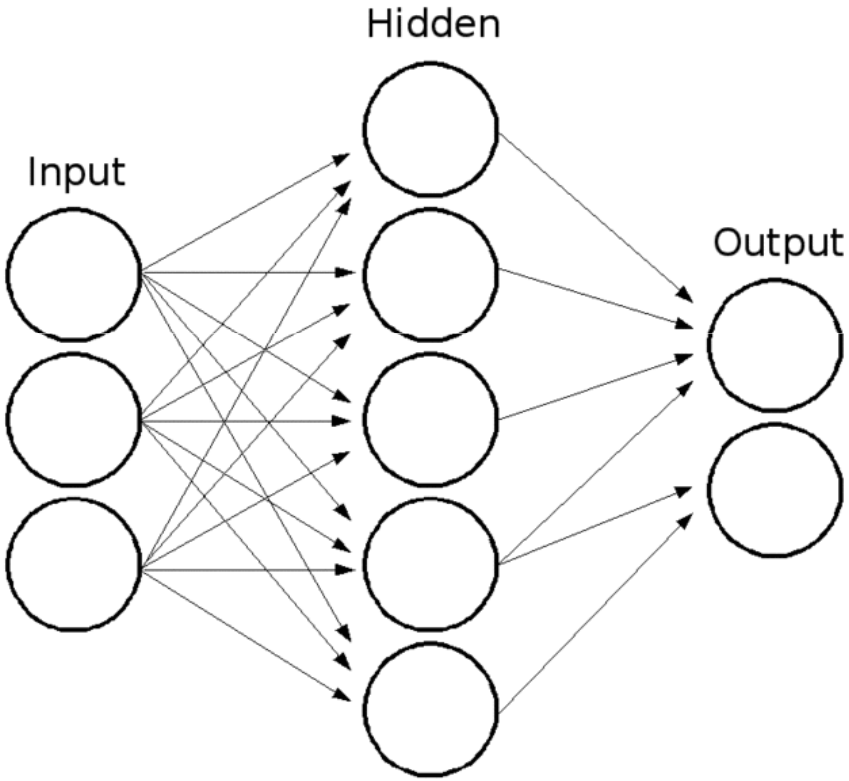
- ANN is an intelligent system
- In ANN, computation occurs in parallel across large numbers of simple processing units, rather than in the serial fashion of traditional computer architectures.
- parallel distributed processing
- learning algorithms and memory
- Experiments and adjustments
- Patient-specific and individual

# ANN structure

- ANN consists of simple interconnected computational nodes, that work like a switch with particular threshold.

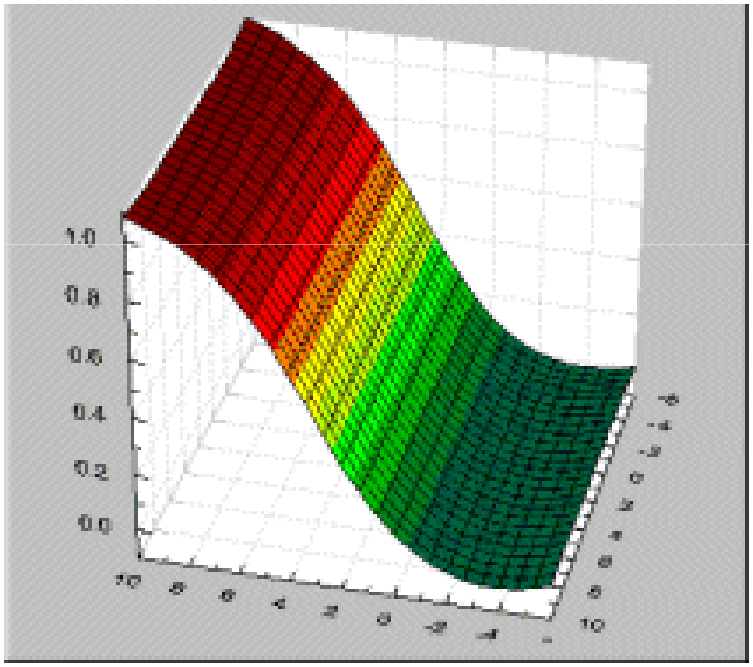
- Input between -1 and +1

- Output between 0 and 1

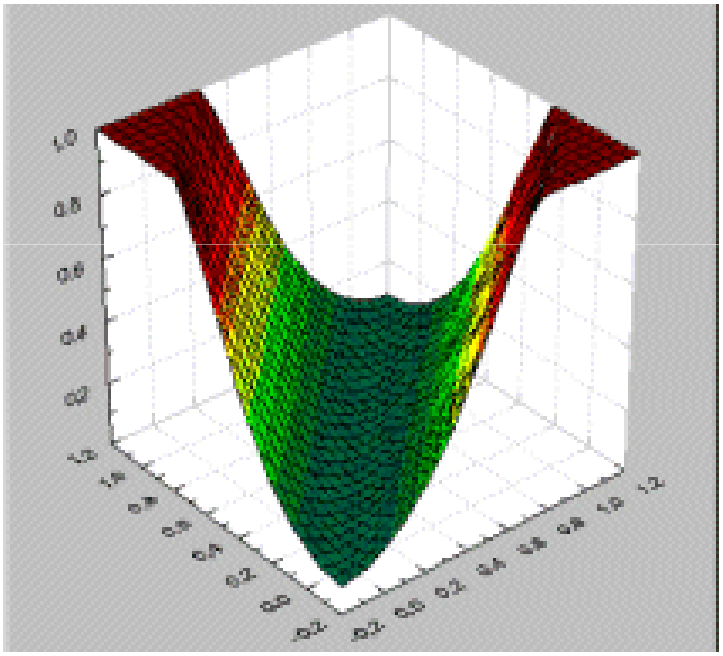


# Network Response Surface

The first activation level is a linear function which is passed through a sigmoid curve

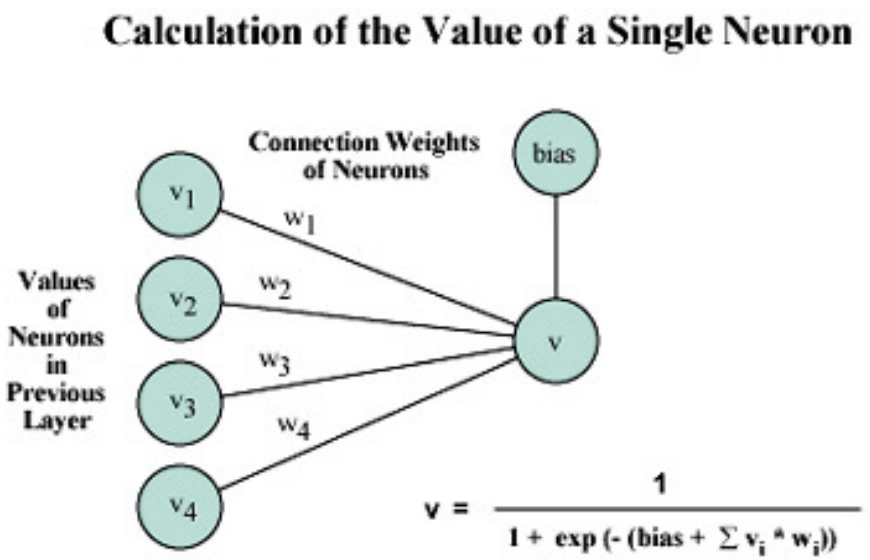


One hidden layer



Two hidden layers

# How ANN works?

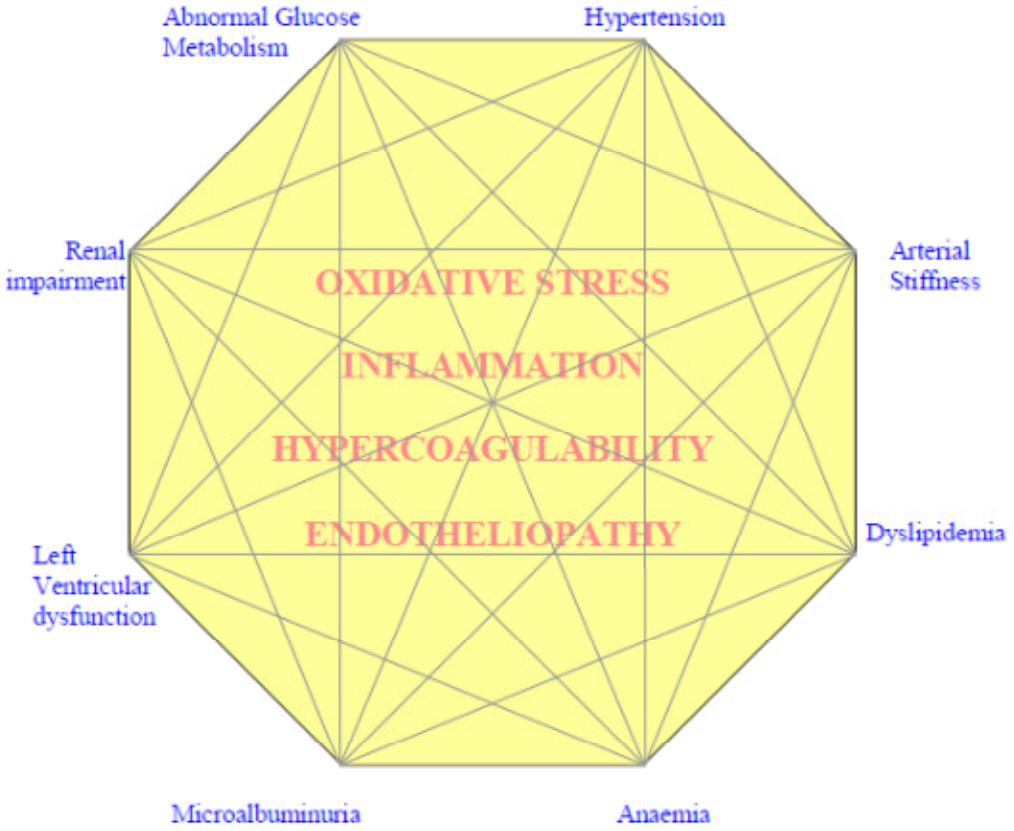



Each neuron sums weighted signals come from previous layer……..
Then weights become adjusted according to the strength of the results until Good predictivity is reached.

*Current Cardiology Reviews*, 2012, *8*, 68-76

# Circulatory Syndrome: An Evolution of the Metabolic Syndrome Concept!

Ali Reza Khoshdel[a,b,*], Shane L.Carney[b] and Alastair Gillies[b]



# 360-degrees Approach

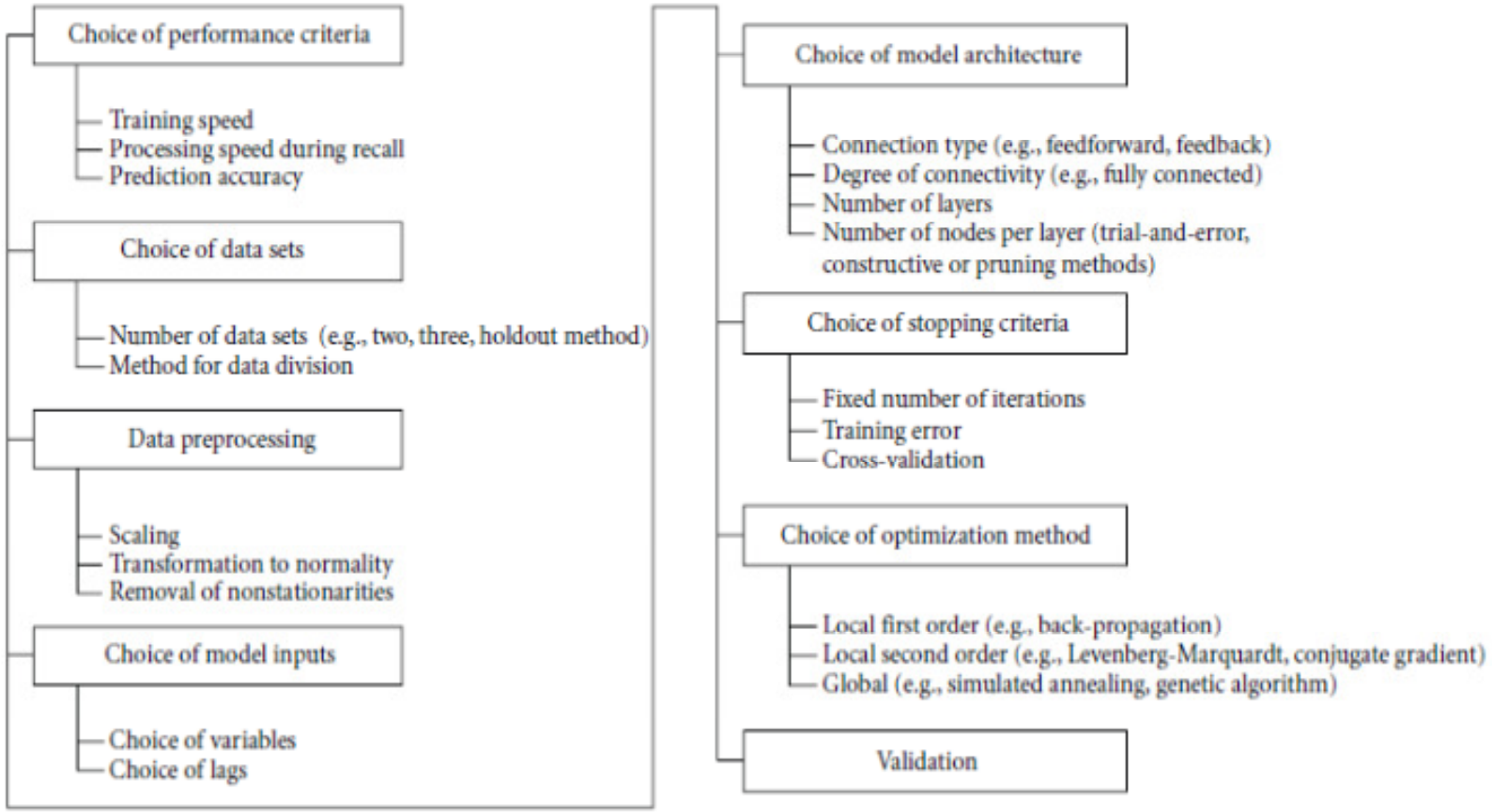
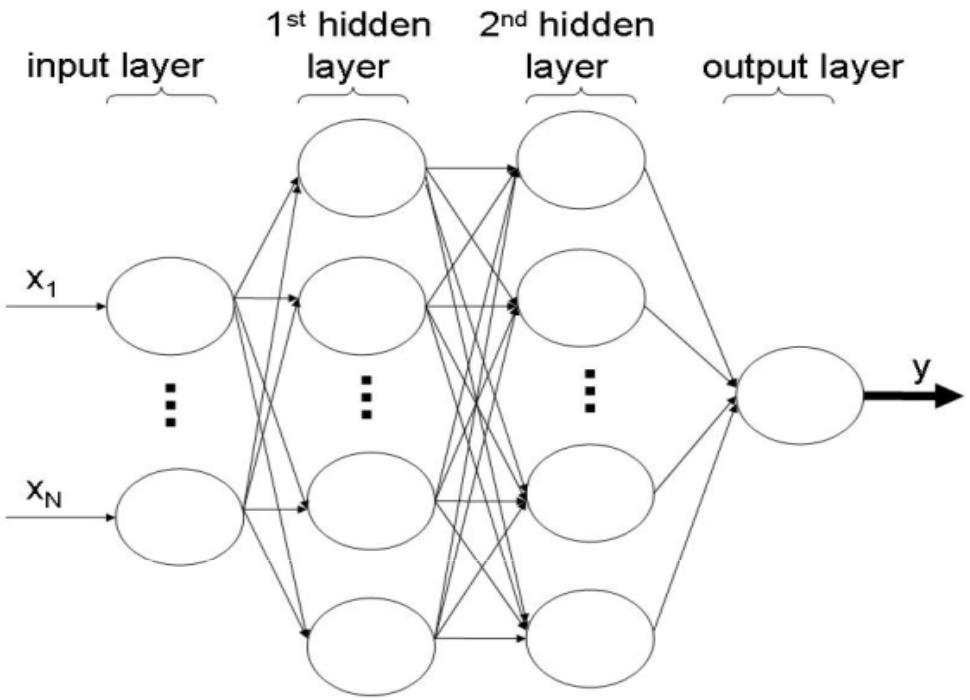



FIGURE 2: The main steps in ANN model development [83].

Hindawi Publishing Corporation
Advances in Artificial Neural Systems
Volume 2009, Article ID 308239, 9 pages
doi:10.1155/2009/308239

# Patients Characteristics

For ANN analysis, 50 characters including the pts' demographics, medical history, medication, urine and blood biomarker tests, hemodynamic and BP profile, and arterial evaluation related to 207 outpatient cases (including 100 DM patients) were included in this study. Average age for the study population was 60± 16 with 55% being male. Twenty six percent had a history of ischemic heart disease, 13% had experienced a previous stroke. They have been followed-up since 2003.




| | | | | |
|---|---|---|---|---|
| **Binary (60)** | **35** | **17** | **8** | **1** |
| **4-levels (60-80-100)** | **38** | **19** | **9** | **4** |

forward feed, back propagation
Error Function: logistic activation function
Classification: confidence limit (for binary outcome)
Classification: Winner-takes-all method (for four-level outcome)

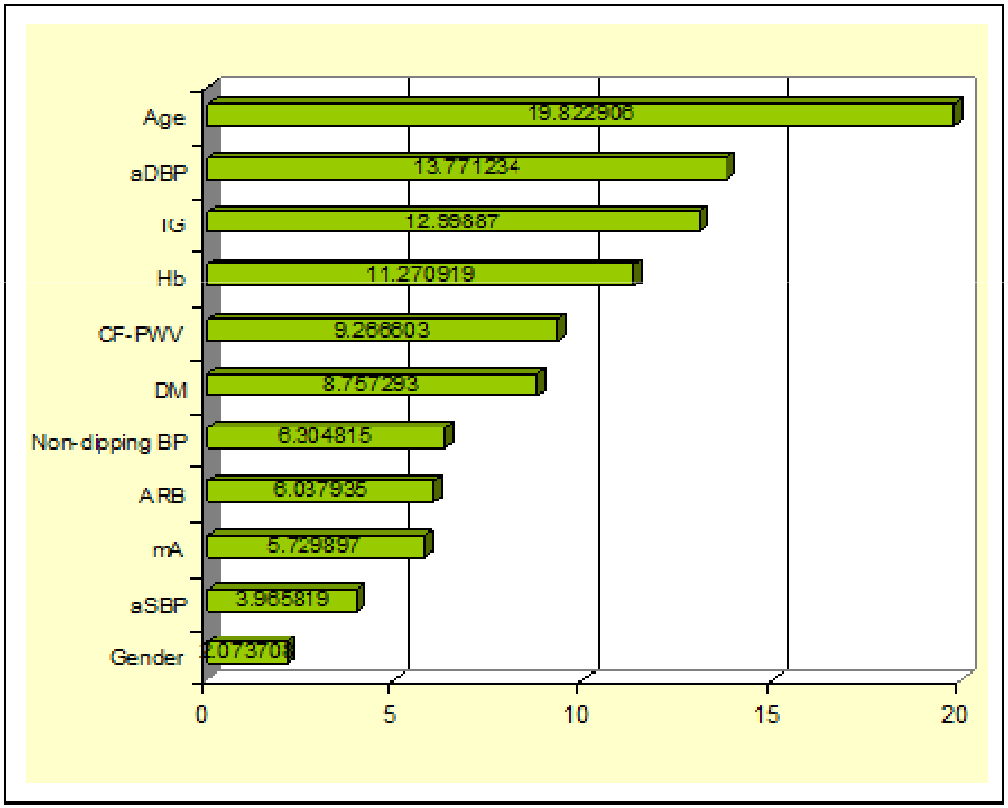
# Training, Validation, Test

Sixty nine, 15 and 16% of the data were randomly selected for the training, validation and test set respectively.
Factors were reduced in refinement phases, with 10 manual backward elimination steps (based on their importance ratio) followed by 10 forward additions of clinically important factors to evaluate their impact on the model performance. Finally **11 factors** with the binary outcome and **12 factors** for the four-level outcome remained for final analysis.

# “PARRS-1 “ based on ANN

**Outcome:**
**GFR ≤60 or >60**

Accuracy
Total: 94.6%
Training: 99.2%
Validation: 86.2%
Test: 83.3%

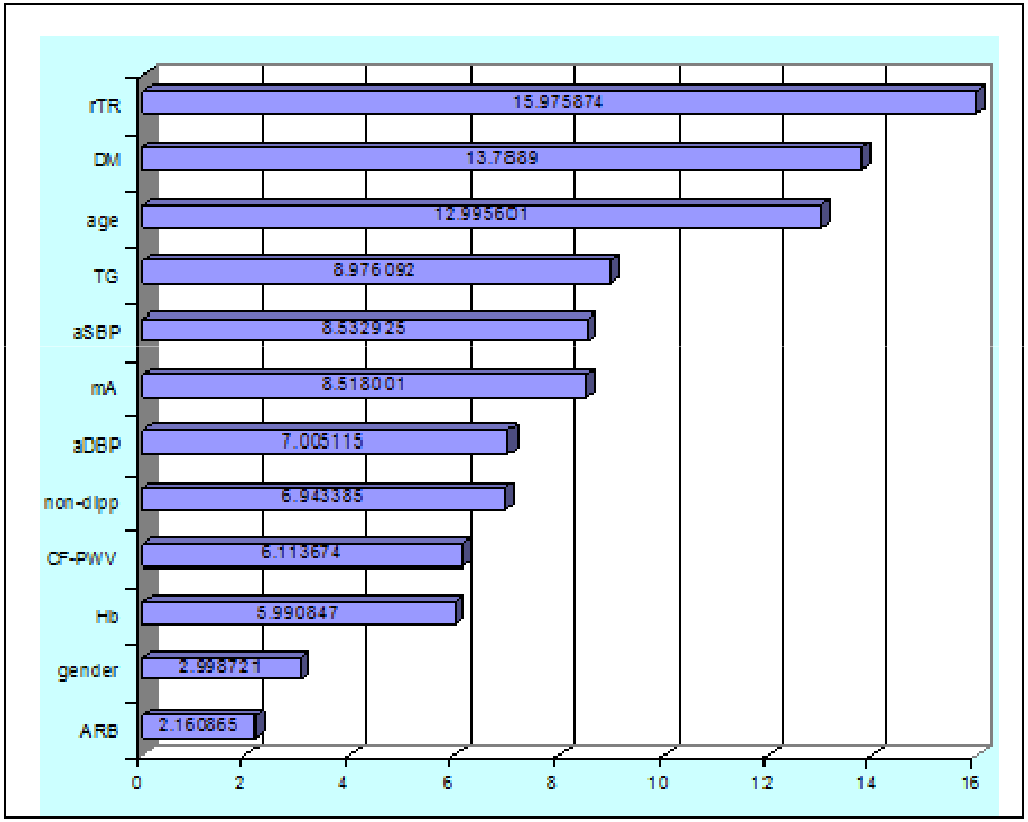



*The most important predictors for GFR (as a binary variable with 60 ml/min as the cut-off point)*

# “PARRS-2 “ based on ANN

**Outcome:**
**GFR >100-80-60>**

Accuracy
Total: 89.2%
Training: 99.2%
Validation: 71.4%
Test: 62.1%



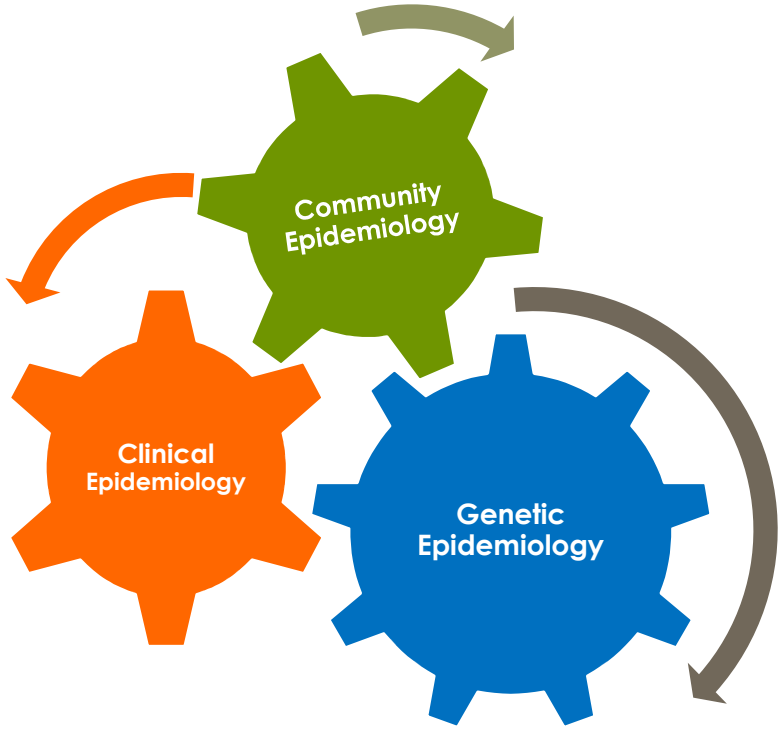

*The most important predictors (max. impact on outcome) for GFR (as a four-level variable with 60, 80 and 100 ml/min as the cut-off points)*

# Conclusion

- Renal Risk Score is an urgent need
- A Post-modern Approach for the score is required
- ANN is an ideal model for risk assessment
- A holistic view is necessary
- Individualization is mandatory
- Notice Central Arterial Function rather than Peripheral blood pressure
- **PARRS** performs well in Renal Risk Assessment
- **Let's go further!**

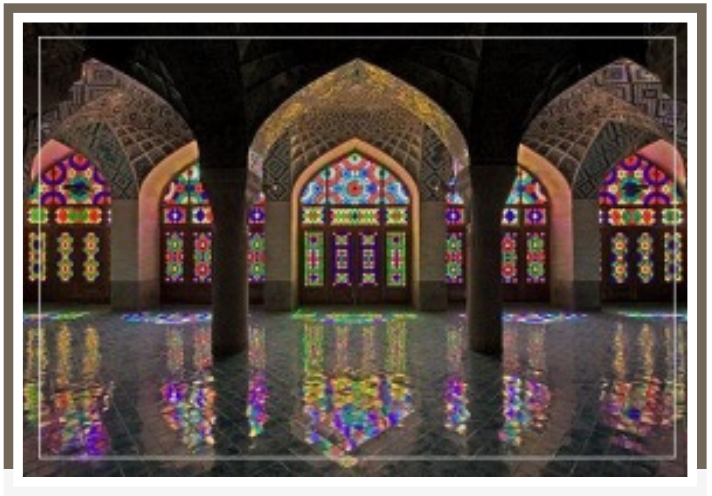
# Future Roadmap

- Assess earlier
- Add genetic Factors
- Consider Microbiom
- Take SEC into account
- Personalize treatments
- Act for Cohort Consortiums
- Multidisciplinary research
- Multidisciplinary training



MERC, AJA University, Tehran, Iran

CCEB, Nobbys Beach, Newcastle, Australia



# Thanks

سپاسگزارم