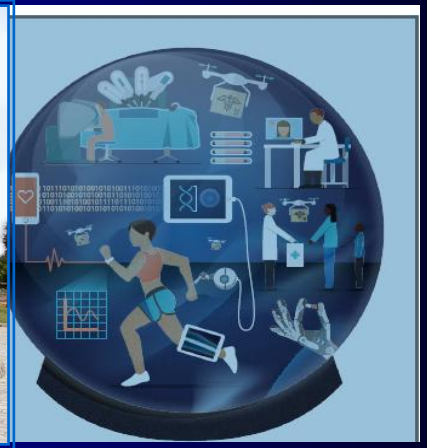
“Advancements in Precision Medicine for Diabetes”



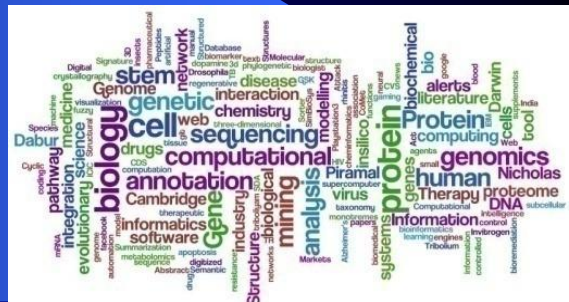
Dr.M.Balasubramanyam

ICMR Emeritus Scientist

Madras Diabetes Research Foundation

(MDRF), Chennai

balumentor@gmail.com



IDF DIABETES ATLAS 11th Edition 2024

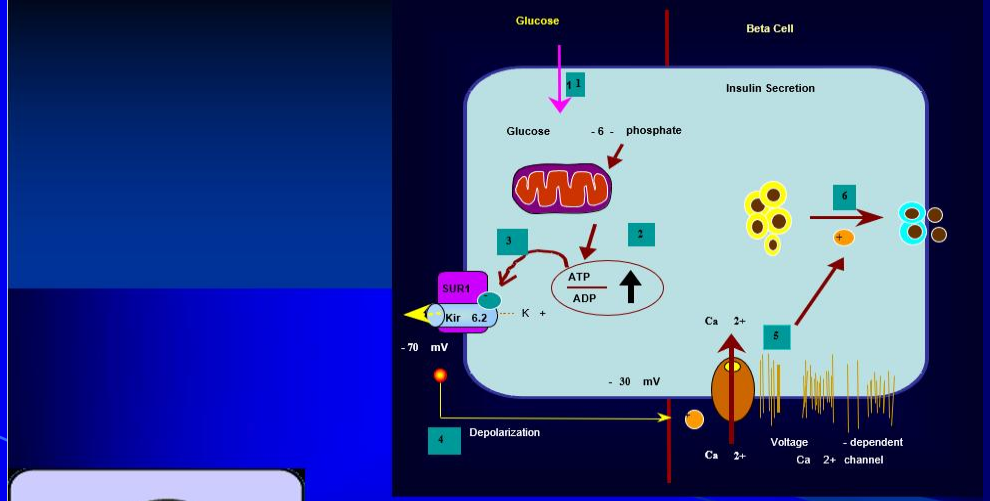
EDITION TO EDITIION - ALARMING ADDITIONS OF DIABETES EVIDENT FROM IDF ATLAS!

Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17)

Anjana et al

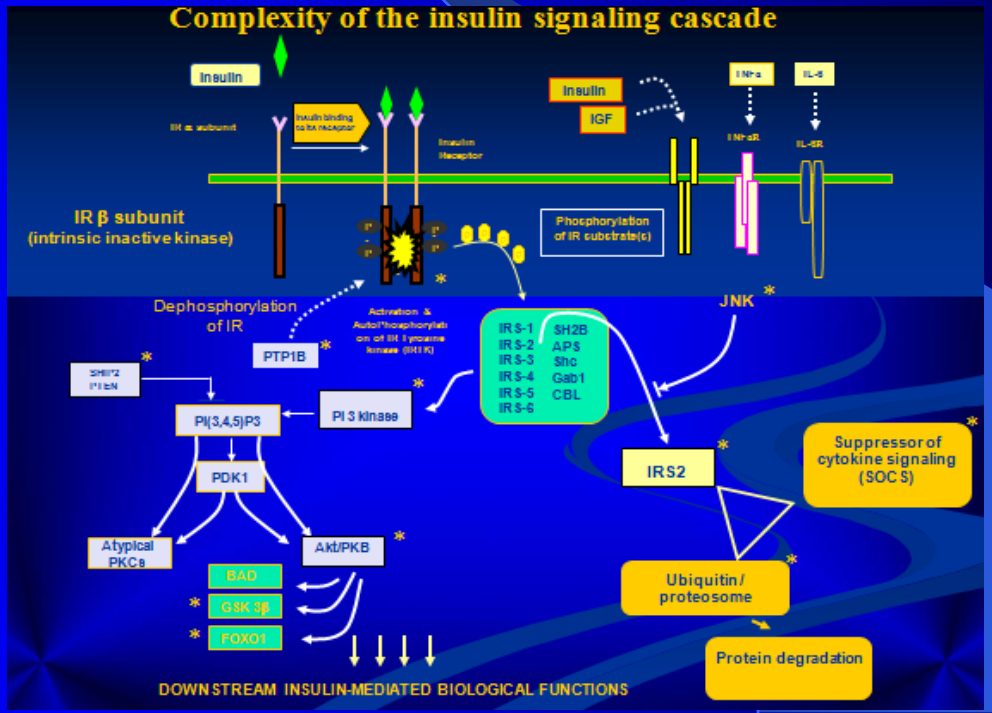
Lancet Diabetes Endocrinol 2023 (7th June)

Projected estimate of diabetes 2023 is 101 millions

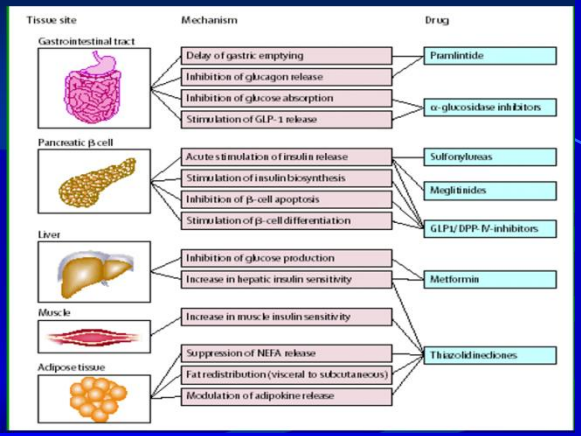


Insulin Secretion cascade

Complexity of the insulin signaling cascade

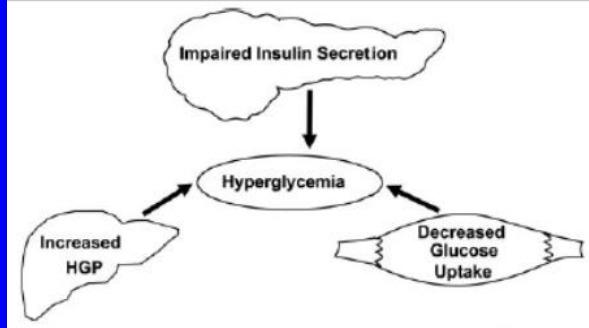


Current anti-diabetic agents and their actions



All Current Treatments for Type 2 Diabetes Have Limitations!

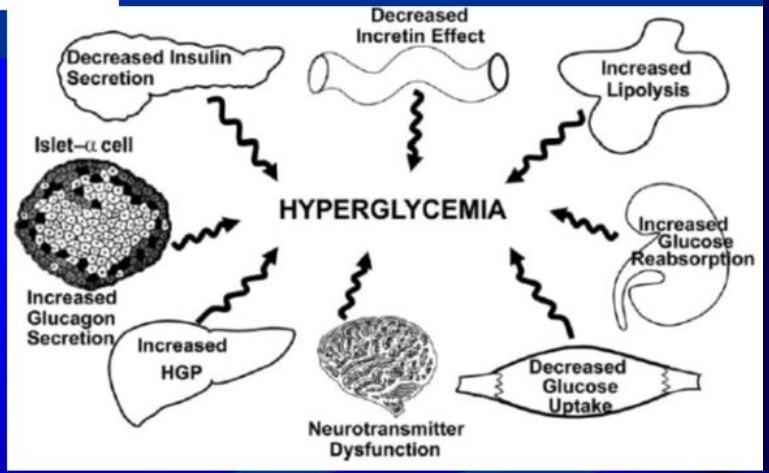
	Sulfonyl-ureas	Insulin	Metformin	Acarbose	Thiazolidi-nediones
Hypoglycemia	□	□			
GI side effects			□	□	
Lactic acidosis			□		
Weight gain	□	□			□
Edema					□
Need LFT monitoring					□
Restricted populations			□		□
Poor responder rate					□
Achieving goals with monotherapy	□		□	□	□



Pathophysiology of Type 2 Diabetes

The triumvirate

The Omnious Octet



Tissues are Issues here !

CELLULAR "STRESS WARS" IN DIABETES

Increased OXIDATIVE STRESS in patients with Type 2 diabetes and its vascular complications

Association of hypoglutathionemia with reduced Na^+/K^+ ATPase activity in type 2 diabetes and microangiopathy — Molecular & Cellular Biochemistry, 2006
Rangasamy Sampathkumar, Muthuswamy Balasubramanyam, Cherian Tara, Mohan Rema and Viswanathan Mohan

Oxidative DNA damage and augmentation of poly(ADP-ribose) polymerase/nuclear factor-kappa B signaling in patients with Type 2 diabetes and microangiopathy — Int. J. Biochem. Cell Biology, 2007
Antonysunil Adaikalakoteswari, Mohan Rema, Viswanathan Mohan, Muthuswamy Balasubramanyam*

Differential gene expression of NADPH oxidase ($p22^{phox}$) and hemoxygenase-1 in patients with Type 2 diabetes and microangiopathy — Diabetic Medicine, 2006
A. Adaikalakoteswari, M. Balasubramanyam, M. Rema and V. Mohan

Subclinical inflammation/oxidation as revealed by altered gene expression profiles in subjects with impaired glucose tolerance and Type 2 diabetes patients — Molecular & Cellular Biochemistry, 2009
Kuppan Gokulakrishnan · Katuva Tulasi Mohanavalli · Finny Monikaraj · Viswanathan Mohan · Muthuswamy Balasubramanyam

Increased INFLAMMATORY STRESS in patients with Type 2 diabetes and its vascular complications

Diabetes is a proinflammatory state: a translational perspective — Expert Rev. Endocrinol. Metab.

Association of C-reactive protein with body fat, diabetes and coronary artery disease in Asian Indians: The Chennai Urban Rural Epidemiology Study (CURES-6)
V. Mohan, R. Deepa, K. Velmurugan and G. Premalatha

Serum levels of interleukin 6, C-reactive protein, vascular cell adhesion molecule 1, and monocyte chemotactic protein 1 in relation to insulin resistance and glucose intolerance—the Chennai Urban Rural Epidemiology Study (CURES)

Association of high sensitivity C-Reactive Protein [hsCRP] and Tumour Necrosis Factor-α [TNF-α] with carotid Intimal Medial Thickness in subjects with different grades of glucose intolerance—The Chennai Urban Rural Epidemiology Study (CURES-31)

Association of Leukocyte Count and hsCRP with Metabolic Abnormalities in Subjects with Normal Glucose Tolerance (CURES – 64)
R Gokulakrishnan, R Deepa, R Sampathkumar, M Balasubramanyam, V Mohan

Subclinical inflammation/oxidation as revealed by altered gene expression profiles in subjects with impaired glucose tolerance and Type 2 diabetes patients
Kuppan Gokulakrishnan · Katuva Tulasi Mohanavalli · Finny Monikaraj · Viswanathan Mohan · Muthuswamy Balasubramanyam

Impaired miR-146a expression links subclinical inflammation and insulin resistance in type 2 diabetes
M. Balasubramanyam · S. Aravind · K. Gokulakrishnan · P. Prabu · C. Sathishkumar · H. Ranjini · V. Mohan

GLYCATION STRESS

DCCT-EDIC findings revealed that:

Early Glycemic control matters!!!

We need to look 'beyond glucose'!!!

Advanced glycation end (AGE) products appear to be an important risk factor independent of glycemic control

Metabolism — A novel advanced glycation index and its association with diabetes and microangiopathy
Rangasamy Sampathkumar, Muthuswamy Balasubramanyam*, Mohan Rema, Chinnaraj Premanand, Viswanathan Mohan

Diabetes Complications — Advanced glycation index and its association with severity of diabetic retinopathy in type 2 diabetic subjects
Balaji Anitha, Rangasamy Sampathkumar, Muthuswamy Balasubramanyam, Mohan Rema*

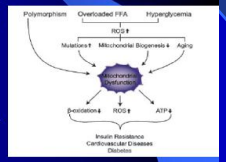
MITOCHONDRIAL STRESS IN DIABETES AND AGING

Glucose and lipid metabolism are largely dependent on mitochondria to generate energy in cells

When nutrient oxidation is inefficient, the ratio of ATP production/oxygen consumption becomes low, leading to an increased production of superoxide anions

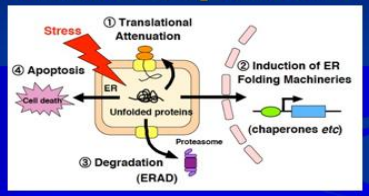
In addition to reactive oxygen species formation, genetic factors, aging, and reduced mitochondrial biogenesis all contribute to mitochondrial dysfunction. These factors also contribute to insulin resistance in classic and non-classic insulin target tissues

Interventions that improve mitochondrial function also improve insulin resistance



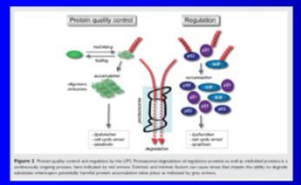
Diabetes as a disease of endoplasmic reticulum stress

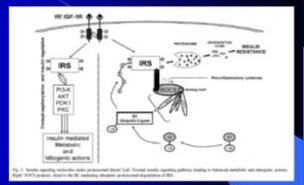
Is there a Protein QC problem in Diabetes?



Indian Journal of Clinical Biochemistry, 2010 / 25 (2) 111-118
REVIEW ARTICLE
ENDOPLASMIC RETICULUM STRESS IN DIABETES: NEW INSIGHTS OF CLINICAL RELEVANCE — Balasubramanyam et al 2010

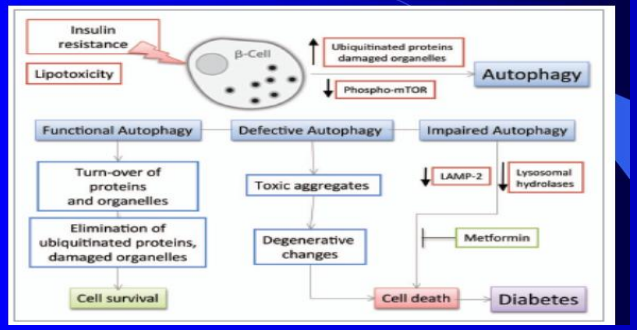
Stressing the ubiquitin-proteasome system
Nico P. Dantuma* and Kristina Lindsten*





Is insulin signaling molecules misguided in diabetes for ubiquitin–proteasome mediated degradation?
Muthuswamy Balasubramanyam, Rangasamy Sampathkumar and Viswanathan Mohan
Madras Diabetes Research Foundation (MDRF), Chennai, India

The emerging role of autophagy in the pathophysiology of diabetes mellitus
Claudio D. Gonzalez,[1] Myung-Shik Lee,[2] Piero Marchetti,[3] Massimo Pietropaolo,[4] Roberto Towns,[5] Maria I. Vaccaro,[6] Hirotaka Watada[7] and John W. Wiley[8,*]



We become so much eccentric and centric in many things!

Glucose-Centric
Insulin-Centric
Pancreas-Centric
Beta-Cell-Centric
Diabetes-Centric

Beyond Glucose
Beyond-VEGF
Beyond-MAU
Beyond-Genetics
Beyond Diabetes

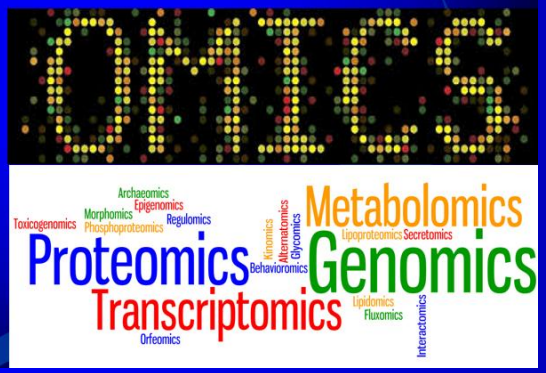
It is evident from DCCT, DCCT-EDIC follow-up, UKPDS and several other Prospective diabetes studies, that diabetic complications could evolve independent of HbA1c and other markers – complexed by a phenomenon of "Metabolic Memory' driven by Epigenetic Modifications

Molecular Pathogenesis of

Type 2 Diabetes

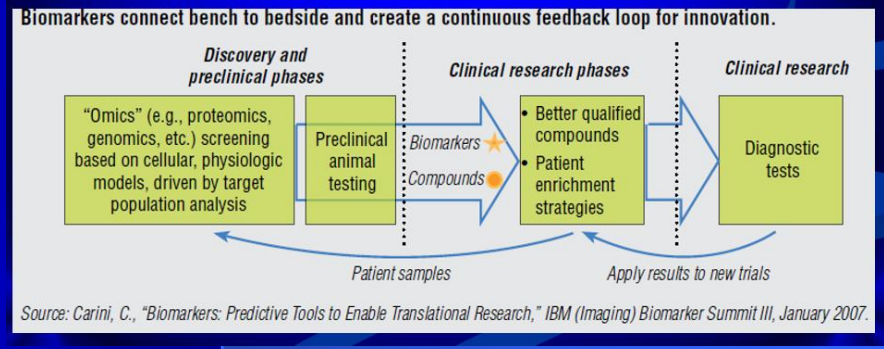
Genes
Behavior
Diet/Nutrition
Infectious agents
Environment
Society
???

Complex problems need sophisticated solutions



Promise of personalized omics to precision medicine

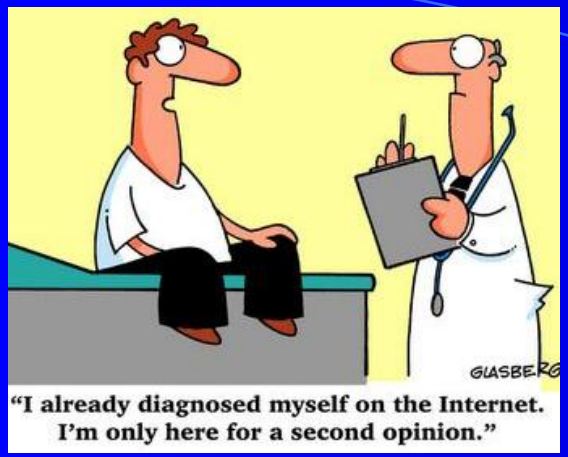
The rapid development of high-throughput technologies and computational frameworks enables the examination of biological systems in unprecedented detail. The ability to study biological phenomena at omics levels in turn is expected to lead to significant advances in personalized and precision medicine. Patients can



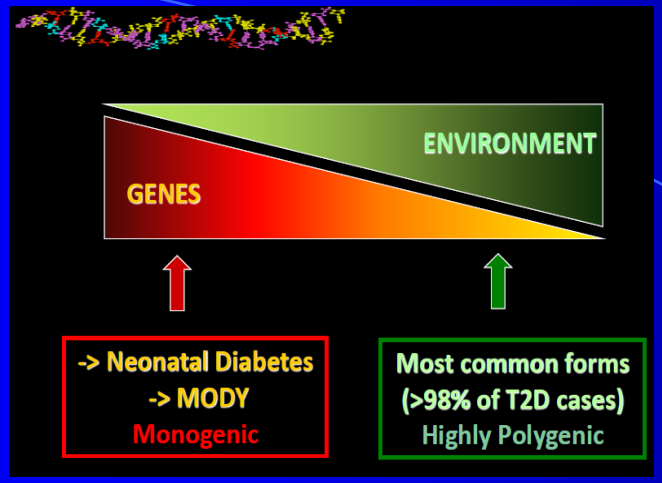
There are several unmet clinical needs in

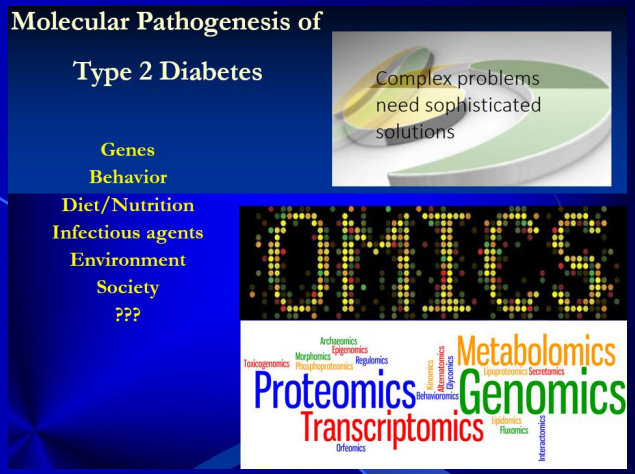
Diabetes Prevention; Prognosis; Diagnosis; Monitoring Therapy Responses; Preventing Diabetic Macro and Microvascular Complications; Managing Youth Type 2 diabetes; Tailoring Precision Medicine & that necessitates

Biomarkers Identification & Omics Research & Data Science



Patients today know more about their diseases. I must get faster modem; higher speed internet; know more about DISEASE-BIOLOGY, BIOMARKERS, OMICS & DATA Science for preventing and treating diseases !!!!





To date, more than 200 genetic loci are associated with the development of multifactorial forms of Type 2 diabetes. However, the proportion of overall trait variance explained by these associated loci is only modest (~5–10%)

Effect sizes of T2D-associated genetic variants are small (OR: 1.1 to 1.4) and predictive value is not greater

However, the genetic studies have implicated new loci in beta-cell function. A lot of biology remains to be done to understand how these new genes affect beta-cell function

Table 1. Genes involved in monogenic diabetes.[a]

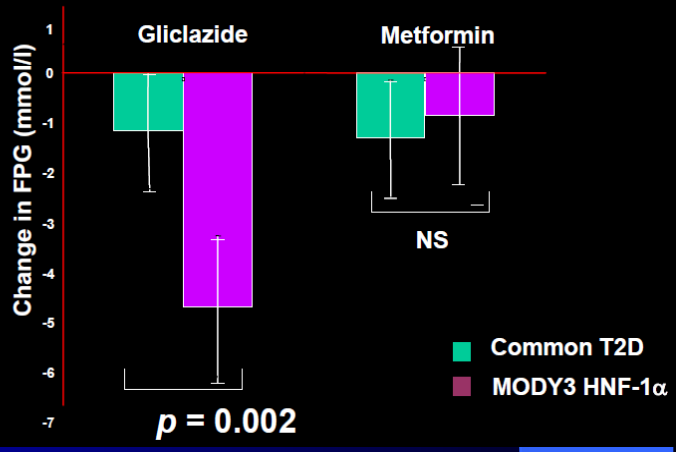
Disease region/gene	Chromosome	Protein/gene function
Insulin secretion defect		
MODY		
HNF4A	20q13.12	β-Cell transcription factor
GCK	7p15.3-p15.1	Glucose sensor
HNF1A	12q24.31	β-Cell transcription factor
PDX1[b]	13 q12.1	β-Cell transcription factor
HNF1B	17q12	β-Cell transcription factor
NeuroD1	2q32	β-Cell transcription factor
Neonatal diabetes		
KCNJ11	11p15.1	β-Cell K_{ATP} channel closure
ABCC8	11p15.1	β-Cell K_{ATP} channel modulator, sulfonylurea response
IDDM2	11p15.5	Insulin production
PTF1A	10p12.31	Pancreatic development
FOXP3	Xp11.23	Immune response control

REMEDY for MODY !!!

MODY

- Correct diagnosis has a major impact on treatment, prognosis and genetic counseling
- Most common causes are mutations in the heterogygous state in HNF1A, GCK, HNF4A and HNF1B (and ABCC8)
- Genetic diagnosis is important for genetic counseling for all forms of MODY
- Genetic diagnosis is important for treatment of HNF1A (SU), GCK (none required), HNF4A (SU) and ABCC8 MODY (SU)

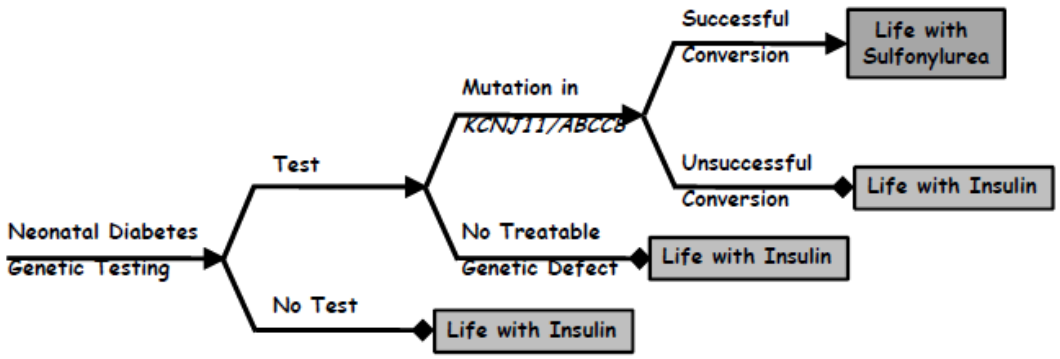
Drug responsiveness: HNF-1α MODY 3 patients are very sensitive to sulphonylureas



Neonatal Diabetes: "Switch insulin to oral drugs"

Mutations in the potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*), gene represent another example in which the genotype directs the approach to specific diabetes treatment. The

Decision Model for Economic Analysis for Genetic Testing in PNDM



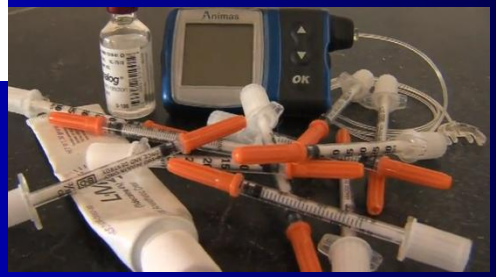
'Miracle' unfolds for diabetic girl

Genetic discovery allows 6-year-old to swap insulin pump for readily available pill

By Peter Gorner
Tribune science reporter

When Lilly Jaffe, 6, gleefully disconnected her insulin pump from her hip last month, her mother, Laurie, forced herself to be brave.

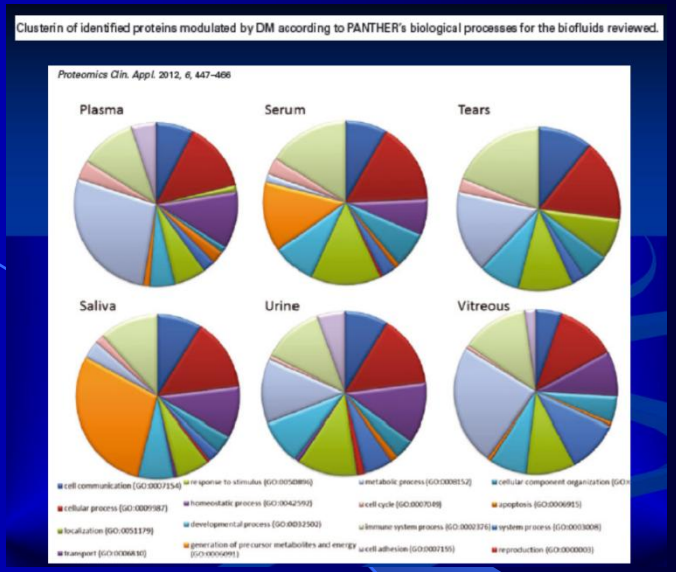
Lilly was cutting the lifeline to the hormone that had kept



NDM caused by *KCNJ11* or *ABCC8* can be « cured »

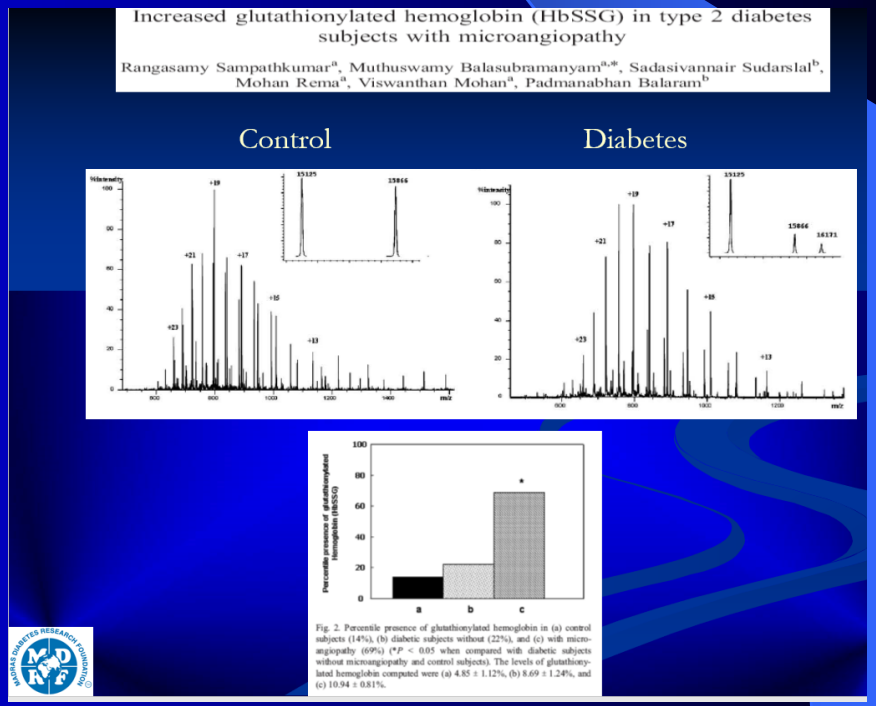
- Most patients with a mutation in a potassium channel gene can be successfully switched from Insulin injections to more efficient oral sulfonylurea treatment.

Proteomics is very close to Drug Discovery and can be profiled in a variety of body fluids. Doctors often see that the protein levels are OK… but individuals exhibit disease or disease-risk. Your adiponectin or HDL levels may be normal… but their biological activity might have lost due to post-translational modification of proteins and therefore knowing these PTMs are important.

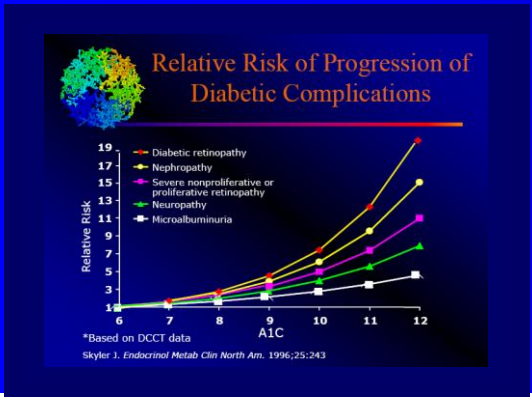


Post-translational modifications (PTMS)

- Phosphorylation
- Glycosylation
- Acylation
- Methylation
- Acetylation
- Ubiquitinylation
- ADP-ribosylation
- Isoprenylation
- Glycation
- Sulfation
- Glutathionylation
- Nitrosylation
- Carboxylation
- Lipdation
- Carbonylation
- Oxidation
- Alkylation
- Hydroxylation
- SUMOlyation
- ISGlyation
- Deamindation
- Racemization
- Isomerization



Monitoring therapy responses in diabetic patients is routinely done by HbA1c measurement which reflect glycemic control over a period of 3 months. Today, glycated albumin is emerging as a tool to measure the glycemic control response in two weeks' time. Collaborating with National Chemical Laboratory, Pune, we have also pioneered and showed Glycated peptides of serum albumin as a biomarker for predicting development of microvascular complications.



Development of Diagnostic Fragment Ion Library for Glycated Peptides of Human Serum Albumin: Targeted Quantification in Prediabetic, Diabetic, and Microalbuminuria Plasma by Parallel Reaction Monitoring, SWATH, and MS^{E*}

Molecular and Cellular Proteomics 2015

Arvind M. Korwar§, Garikapati Vannuruswamy§, Mashanipalya G. Jagadeeshaprasad§, Ramesha H. Jayaramaiah§, Shweta Bhat§, Bhaskaran S. Regin‡, Sureshkumar Ramaswamy§, Ashok P. Giri§, Viswanathan Mohan‡, Muthuswamy Balasubramanyam‡, and Mahesh J. Kulkarni§¶

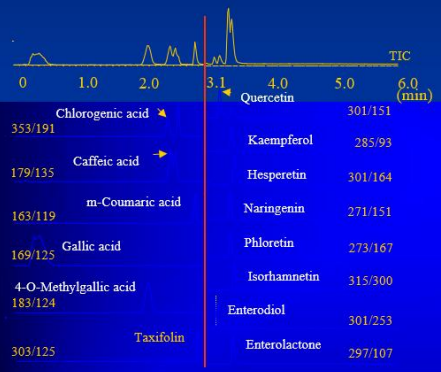
Medical News TODAY

predominant AGEs, constituting up to 80% of total AGEs" he adds. "The association of CML modified peptides of albumin with prediabetes, diabetes, and microalbuminuria is a clinically relevant and therapeutically important finding" says Balasubramanyam. Heterogenous AGEs, particularly CML has been shown to predict the development of microvascular complications of diabetes independent of HbA1c in the DCCT (Diabetes Control and Complications Trial) study. Very recently increased CML-AGEs have been shown to predict incident diabetes also.

Glycated albumin - a promising marker for diabetes and glucose control

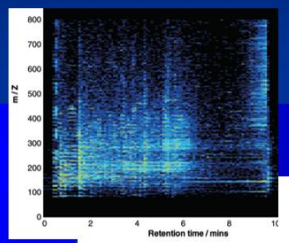
Two metabolomic approaches

Targeted metabolomics

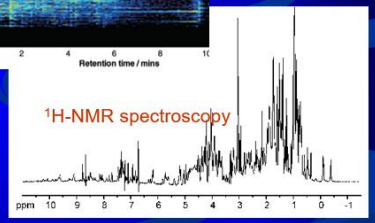


Biomarker quantification

Untargeted metabolomics



Mass spectrometry



Biomarker discovery

Nat Med. 2011 April ; 17(4): 448–453. doi:10.1038/nm.2307.

Isoleucine, leucine, valine, tyrosine & phenylalanine

Metabolite Profiles and the Risk of Developing Diabetes

Today it is well conceived that apart from hypertriglyceridemia and hyperinsulinemia – diabetes pathogenesis is also linked to hyper-aminoacidemia.

Get ready for an 'ACID' test for diabetes: Metabolomics Magic!

hyperaminoacidemia

Scientific Reports, 2018

Serum metabolite profile associated with incident type 2 diabetes in Koreans: findings from the Korean Genome and Epidemiology Study

Soo Jin Yang[1], So-Young Kwak[2], Garam Jo[2], Tae-Jin Song[3] & Min-Jeong Shin[2]

Of all metabolites measured, 22 were significantly associated with T2D risk. Specifically, serum levels of alanine, arginine, isoleucine, proline, tyrosine, valine, hexose and five phosphatidylcholine diacyls were positively associated with T2D risk, whereas lyso-phosphatidylcholine acyl C17:0 and C18:2 and other glycerophospholipids were negatively associated with T2D risk. The associated metabolites were further correlated with T2D-relevant risk factors such as insulin resistance and triglyceride indices. In

Circulating MiRNAs of 'Asian Indian Phenotype' Identified in Subjects with Impaired Glucose Tolerance and Patients with Type 2 Diabetes

PLOS ONE, 2015

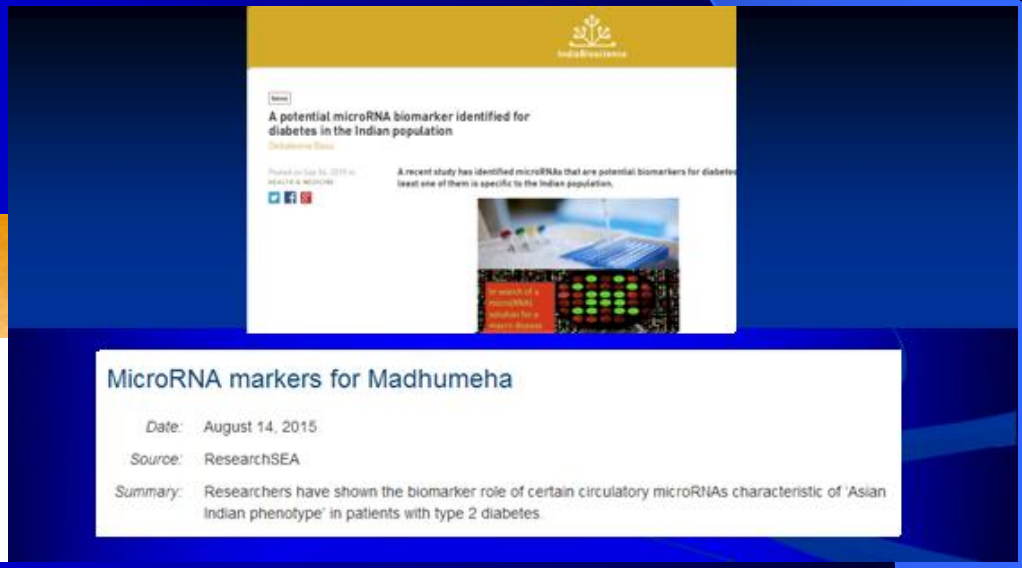
Paramasivam Prabu[1], Sophie Rome[2], Chandrakumar Sathishkumar[1], Sankaramoorthy Aravind[1], Balakumar Mahalingam[1], Coimbatore Subramanian Shanthirani[1], Caroline Gastebois[2], Audrey Villard[2], Viswanathan Mohan[1], Muthuswamy Balasubramanyam[1]*

List of differentially expressed circulating miRNAs

Groups	miRNAs	Fold changes	p value
NGT vs IGT	hsa-miR-128	1.42	0.041
	hsa-miR-99b-5p	1.41	0.028
IGT vs T2DM	hsa-miR-130b-3p	1.41	0.035
	hsa-miR-142-3p	0.57	0.0041
	hsa-miR-374a-5p	0.58	0.039
	hsa-miR-423-5p	1.54	0.011
	hsa-miR-484	1.37	0.004
	hsa-miR-629-5p	1.84	0.03
NGT vs T2DM	hsa-let-7d-3p	1.26	0.029
	hsa-miR-128	1.5	0.047
	hsa-miR-130b-3p	1.46	0.049
	hsa-miR-142-3p	0.65	0.039

- **Considering microRNAomics, we have reported a panel of altered miRNAs of Asian Indian phenotype not only in patients with type 2 diabetes but also in individuals with prediabetes.**

Our work got excellent media coverage quoting 'Tiny RNA molecules as diabetes marker' & "MicroRNA markers for Madhumeha".

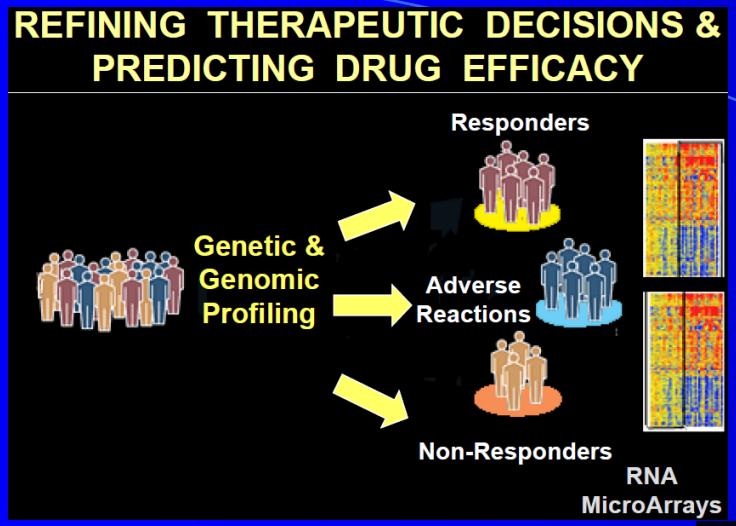


nature INDIA

doi:10.1038/nindia.2015.86 Published online 29 June 2015

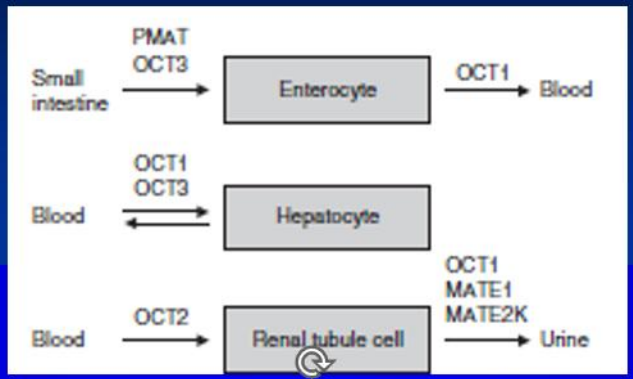
Tiny RNA molecules as diabetes marker

Researchers have identified a specific microRNA (miRNA) that has higher serum levels in people with prediabetes and type 2 diabetes than healthy individuals[1]. Thus, the serum levels of this miRNA could be monitored to predict the risk and onset of type 2 diabetes.



Pharmacogenomis

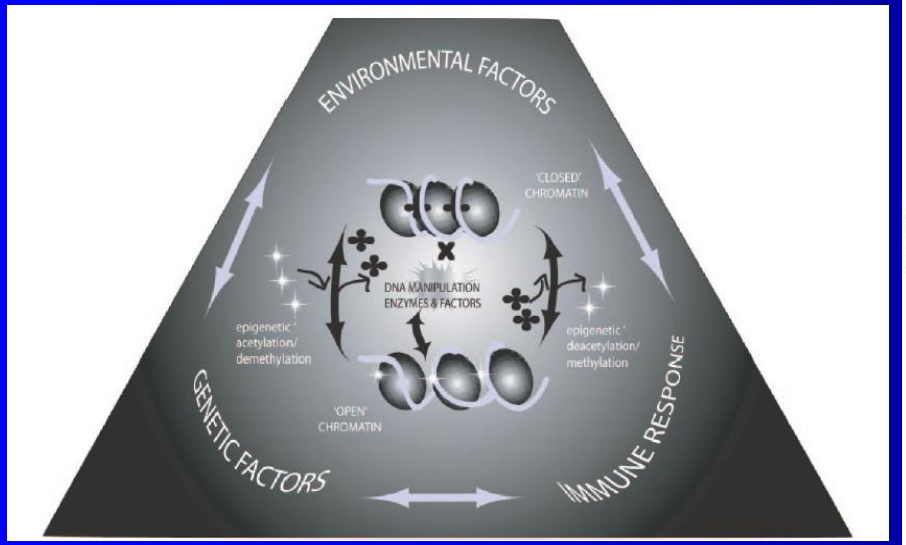
Specific transporters are involved in intestinal absorption, hepatic uptake and renal excretion of metformin

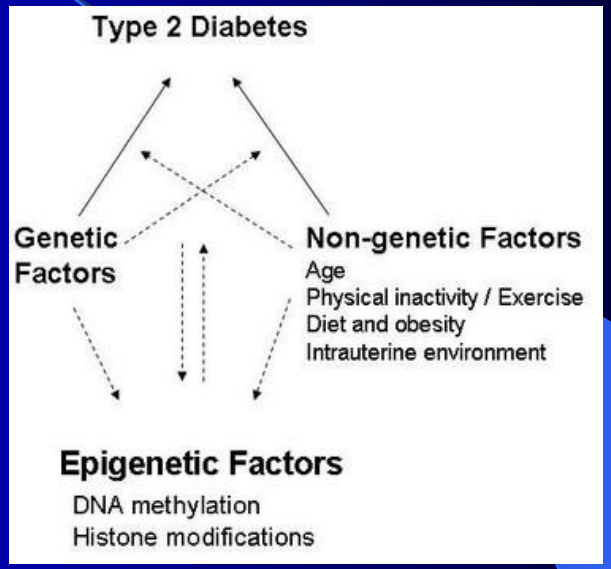


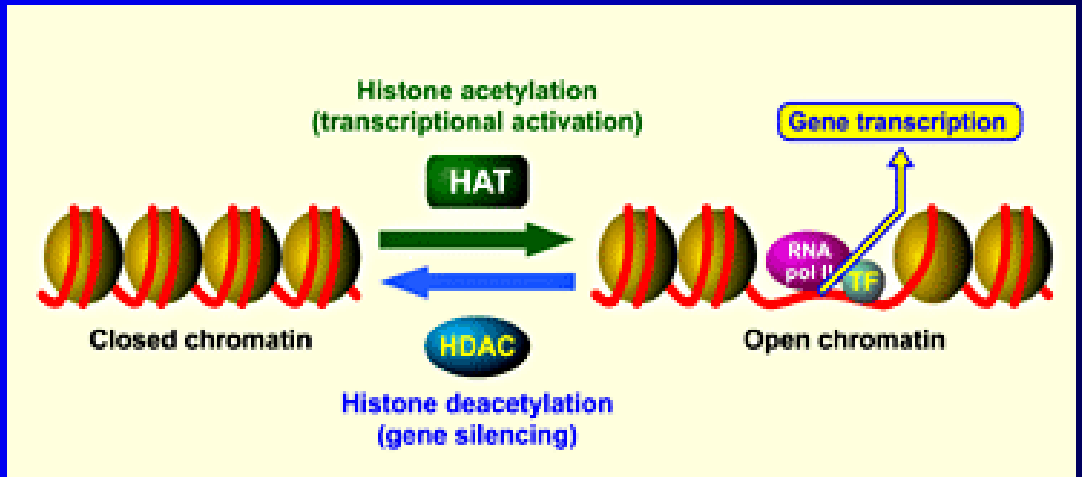
A variant in OCT1 shown to decrease response to metformin

A variant in MATE1 produces a small increase in the hyperglycemic effect of metformin

Recently, it has become increasingly clear that part of the gene–environmental interactions relevant for complex diseases such as Type 2 diabetes is regulated by epigenetic mechanisms such as histone modifications and DNA methylation







Recently, it has become increasingly clear that part of the gene–environmental interactions relevant for complex diseases such as Type 2 diabetes is regulated by epigenetic mechanisms such as histone modifications and DNA methylation

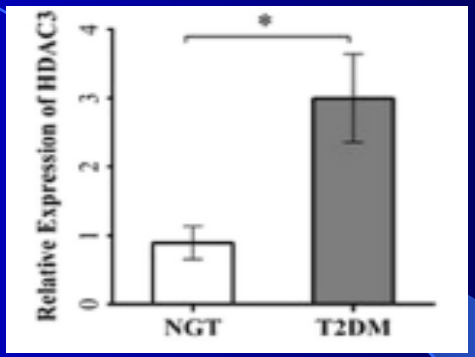
Sathishkumar et al. Clinical Epigenetics (2016) 8:125
DOI 10.1186/s13148-016-0293-3

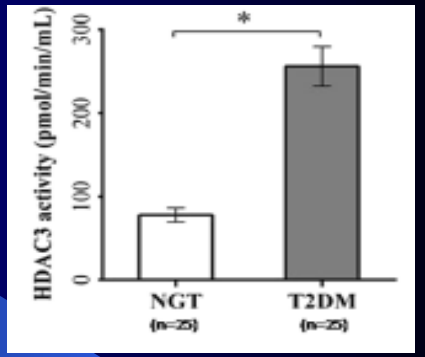
Clinical Epigenetics

RESEARCH Open Access

Augmentation of histone deacetylase 3 (*HDAC3*) epigenetic signature at the interface of proinflammation and insulin resistance in patients with type 2 diabetes

Chandrakumar Sathishkumar, Paramasivam Prabu, Mahalingam Balakumar, Raji Lenin, Durai Prabhu, Ranjith Mohan Anjana, Viswanathan Mohan and Muthuswamy Balasubramanyam*





Promising Epigenetic Drug Target for Diabetes - Newswise

www.newswise.com/articles/view/669131?print-article

Feb 8, 2017 - **Promising Epigenetic** Drug **Target for Diabetes** ... be the way for future anti-**diabetic** drugs with novel mode of actions and newer therapeutic options", said Muthuswamy **Balasubramanyam**, Dean of Research Studies & Senior Scientist from the Madras **Diabetes** Research Foundation in Chennai, India.

Sathishkumar et al. Human Genomics (2018) 12:41
https://doi.org/10.1186/s40246-018-0173-3

Human Genomics

PRIMARY RESEARCH Open Access

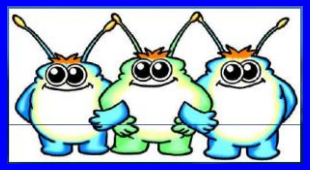
Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes

Chandrakumar Sathishkumar, Paramasivam Prabu, Viswanathan Mohan and Muthuswamy Balasubramanyam*

ALTERED LNCRNAS SIGNIFY AN UPSTREAM LINK IN THE ETIOLOGY OF TYPE 2 DIABETES

15 OCTOBER 2018 | DIABETES

Researchers from the Madras Diabetes Research Foundation (MDRF), Chennai, India have unraveled a new-biology link in the etiology of type 2 diabetes as their work[1] demonstrated an association of altered long non-coding RNAs (LncRNAs) with accelerated senescence, inflammation and insulin resistance in patients with type diabetes.



One more layer of complexity……. Metagenomics!

Your diabetes fate is not only decided by your own genes but also by your gut microbial genome !!!

Biology and Medicine

Balasubramanyam, Biol Med 2014, 6:4
http://dx.doi.org/10.4172/0974-8369.1000220

Short Communication Open Access

Metagenomics Health Claim: Are you Rich Enough in your Gut Micro biota?

Muthuswamy Balasubramanyam*

Dean of Research Studies & Senior Scientist, Department of Cell & Molecular Biology, Madras Diabetes Research Foundation, No.4, Conran Smith Road, Gopalapuram, Chennai - 600086, India

clinical impact on gut microbiota manipulation. To conclude, better health may not directly be related to how rich you are (financially)… but it's going to be related to how rich you are in your gut microbiota! Therefore the new advice for both the general public and the patients is this– 'stock up on your good gut bacteria!' The road to personalized gut microbiota management might be seen long and winding, but the destiny makes it worthwhile with a futuristic research and development investment.

Indo-Danish grant on Gut Microbiome and Diabetes

We just completed a large scale Indo-Danish metagenomics project – where we have shown distinct alterations of gut microbiome diversity not only in patients with diabetes but also in prediabetes. In addition, we do find ethnicity specific differences in gut microbiome.

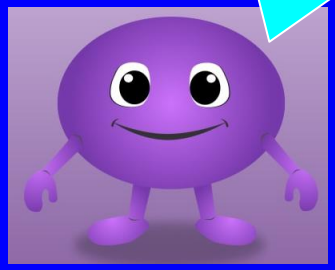
Trans-ethnic gut microbial signatures of prediabetic subjects from India and Denmark

Pinna et al. Genome Medicine (2021) 13:36

Trans-ethnic gut microbiota signatures of type 2 diabetes in Denmark and India

Pinna et al..Genome Medicine (2021) 13:37

Taking a Diet?.....
Eat for you and
Eat for me too….



Microbial Health…..& Microbial Richness….

Detrimental Impact of Microbiota-Accessible Carbohydrate-Deprived Diet on Gut and Immune Homeostasis: An Overview

Frontiers in Immunology, 2017

Claire Immediato Dalen[1,2,3], Gabriela Veronica Pinget[1,2], Jian Kai Tan[4] and Laurence Macia[1,2,4]*

Eat for your Gut Microbiome and Choose MAC diet! – Your Health is guaranteed and insured too!

Dr. M. Balasubramanyam
Dean of Research Studies & Senior Scientist
Madras Diabetes Research Foundation, Chennai-600086, India
Corresponding Author: Dr. M. Balasubramanyam; baluglobaldiab@gmail.com

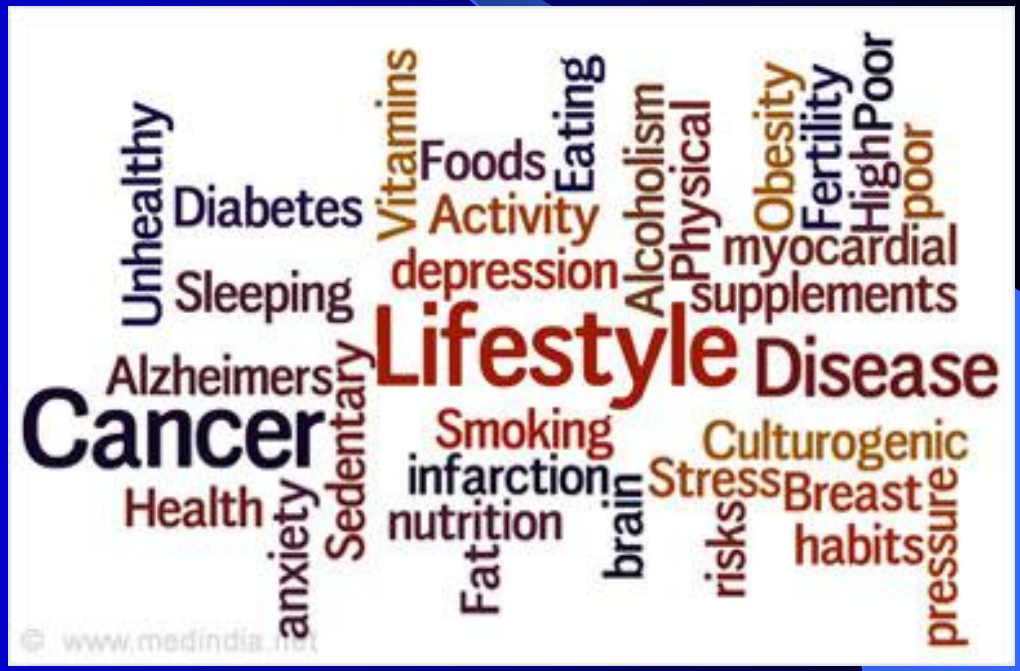
Diet plays an important role in shaping the structure and function of the gut microbiota. The microbes and microbial products in turn can influence various aspects of host physiology. One promising route to affect host function and restore health is by altering the gut microbiome using dietary intervention. We are what we eat and that's why everyone is prescribed for healthy food choice. Do you know the food we eat plays an essential role in maintaining the richness and function of our gut microbiota (trillions of bacteria that live within our digestive tract) and thereby dictates our health and keeps us disease-free?

Want to be Healthy? – Choose MAC diet: Much of the carbon and energy for members of the microbiota originate from plant- and animal-derived dietary carbohydrates and plant fibres (resistant to degradation and absorption by the host). Microbial competition within the gut is intense for metabolic access to the energy and carbon sequestered in these molecules. The complex carbohydrate portion of dietary fibre that can be metabolized by gut microbes, were proposed to be referred by the term "microbiota-accessible carbohydrate" (MAC). MACs serve as selective agents, altering the composition of the microbiota, but also dictate the functionality and metabolic output. Short-chain fatty acids (SCFAs), namely, acetate, butyrate, and propionate, are released by gut bacteria during fermentation of dietary fibers; they operate through specific receptors on the host and offer several metabolic benefits. When we adapt to MAC-deprived diet, we also lose the metabolic benefits of gut-microbiome derived metabolites.

It's true – Modern Society consume MAC-deprived diet: Modern diet consists of heavily processed foods, rich in fat, sugar, protein, and a variety of additives, while remaining low in micronutrients and dietary fiber. The recommended daily intake of dietary fiber is at least 30 g, although, on average, those on the Western diet only consume 15 g. People in traditional societies (for example, Hadza hunter-gatherers of Tanzania) where fiber intake can reach 50–120 g/day, are associated with a much more diverse gut microbiota when compared with people in Western countries. A diverse microbiome (microbiome richness) is associated with "good health," while low diversity and micrbiome dysbiosis have been correlated to several non-communicable diseases including type 2 diabetes.

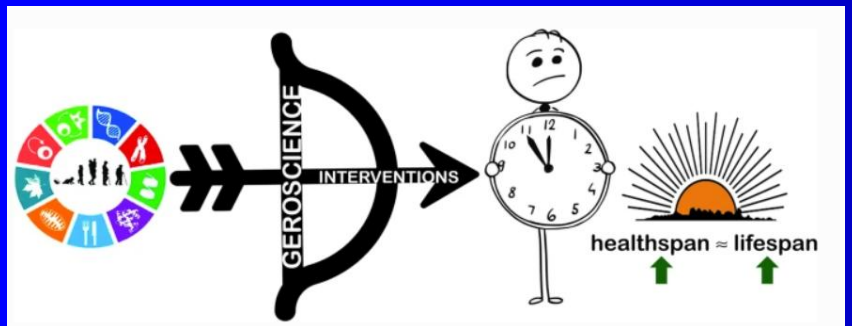
Low consumption of MACs over generations leads to the complete disappearance of beneficial bacterial strains in a preclinical mice model study. If we extrapolate this finding, this seems to suggest that long-term-reduced MAC consumption over generations will likely to have detrimental effects in humans. *The message is clear* – Choose MAC diet, if needed combine dietary and probiotic interventions, keep your gut microbiome happy; they in turn make you happy, healthy and keep you free from lifestyle diseases.

Health is Under Threat & Healthy Aging is a Dream



Lifespan is increasing.....What about Health span?

Dr. M. Balasubramanyam
Dean of Research Studies & Senior Scientist, MDRF



healthspan. Studies are underway worldwide to use the discoveries about calorie restriction and other related genetic or pharmacological interventions to close that 20 to 30-year gap between lifespan and 'healthspan'. Big Pharma already have an 'eye' on the development of "healthspan-enhancing pharmaceuticals". After all, we have made great progress in extending the length of life and now must focus on the quality of those added years.

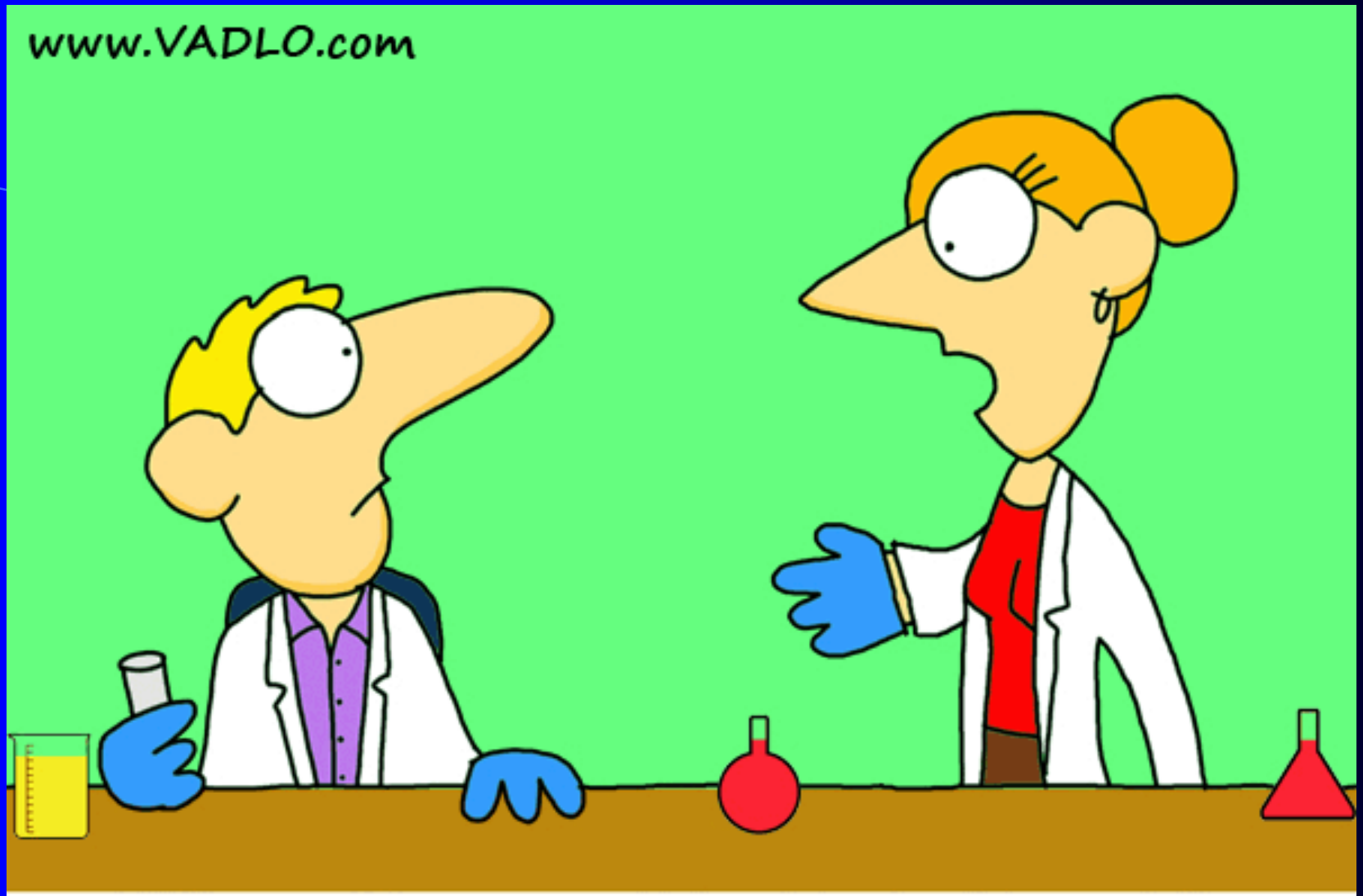
Open Longevity Science, 2013, *7*, 1-10

Open Access

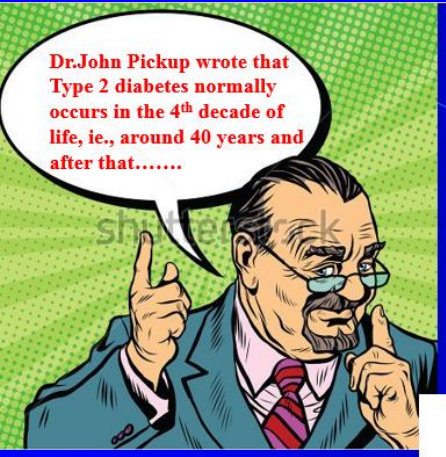
Research and Policy to Achieve Healthy Aging in Asia: Recommendations from an Expert Workshop

Ng Tze Pin[1], Balasubramanyam Muthuswamy[2], Fenech Michael[3], Head Richard[4] Amarra Maria Sofia*,[5] and Loke Seng Cheong[6]

- Consortium for Ageing Research and Education in Asia (CARE-ASIA)
- Asia Pacific Ageing Consortium (APAC).

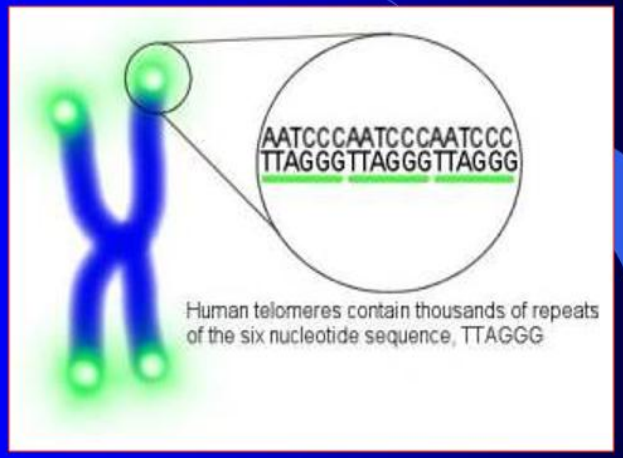


"All my colleagues are doing "Ageing Research",
I am simply ageing!"



Then why do we get type 2 diabetes even around the 2nd and 3rd decade of our life ??????

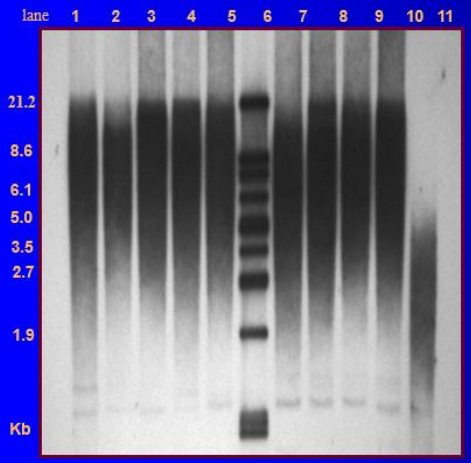
Telomere shortening -an emerging, long-term biomarker of lifestyle diseases ? -- marker of accelerated (Biological) Aging

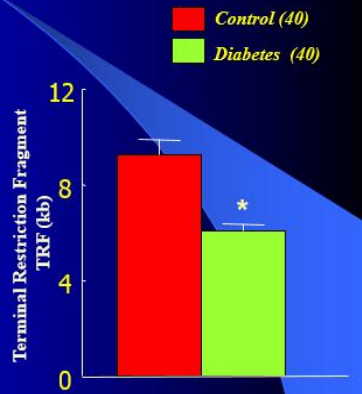


Telomeres are highly susceptible to oxidative stress

Telomere shortening occurs in Asian Indian Type 2 Diabetic patients

Adaikalakoteswari et al. 2005, Diabetic Medicine



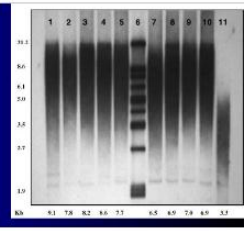


* P = 0.001 compared to Control

Telomere shortening occurs in Asian Indian Type 2 diabetic patients

Diabetes Medicine 2005

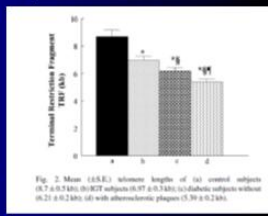
A. Adaikalakoteswari, M. Balasubramanyam and V. Mohan



Association of telomere shortening with impaired glucose tolerance and diabetic macroangiopathy

Atherosclerosis 2007

Antonysunil Adaikalakoteswari, Muthuswamy Balasubramanyam*, Radhakrishnan Ravikumar, Raj Deepa, Viswanathan Mohan



Telomere shortening & metabolic/vascular diseases

Indian Journal of Medical Research 2007

M. Balasubramanyam, A. Adaikalakoteswari, S. Finny Monickaraj & V. Mohan

Short Leukocyte Telomere Length Predicts Risk of Diabetes in American Indians: The Strong Heart Family Study

Jinying Zhao,[1] Yun Zhu,[1] Jue Lin,[2] Tet Matsuguchi,[2] Elizabeth Blackburn,[2] Ying Zhang,[3] Shelley A. Cole,[4] Lyle G. Best,[5] Elisa T. Lee,[3] Barbara V. Howard[6]

Diabetes, 2013

Hi…. You are absolutely wrong!
At the age of 40, I have all kinds of health problems… First, I got diabetes; It brought me all of its companions. I have a long waiting list to see specialists in the next 3 to 6 months. Even in sleep, I see only Lab reports, Scans, X-rays, colorful tablets and capsules, diet advice, exercise-threat and loads of medical bills…prepaid and postpaid…Recently, I met a Disease-Biologist… He says my biologicial age is 50 plus! and I must be running through

ACCELERATED AGING!!!!!!

Hi Friend, you must be lucky… You know every single speciality doctor in the City…. You must be Healthy!

RISE study Raise New Concerns on Youth Diabetes Treatment!

ADA-2018

Youth-Onset Diabetes Needs Different Approach to That in Adults
Diabetes Much More Aggressive in Teens
T2D Diagnosis at Younger Age: 'Scary Stuff'

In adolescents with impaired glucose tolerance (prediabetes) or recent-onset type 2 diabetes, early intervention with long-acting insulin followed by metformin, or metformin alone — both given for a year — failed to prevent deterioration in beta-cell function. Indeed, beta-cell function declined in both groups during treatment and worsened after treatment. Additionally, youth with IGT and T2D, compared to adults, are more insulin resistant.

Association of increased levels of MCP-1 and cathepsin-D in young onset type 2 diabetes patients (T2DM-Y) with severity of diabetic retinopathy *Journal of Diabetes and Its Complications* (2017).

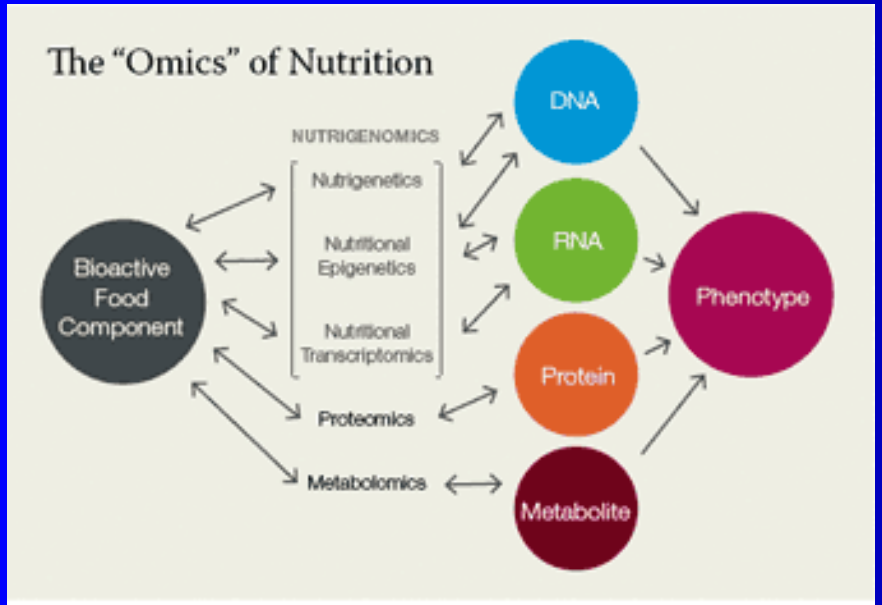
Sruthi Reddy [a], Anandakumar Amutha [a], Ramachandran Rajalakshmi [a], Regin Bhaskaran [a], Finny Monickaraj [b], Sampathkumar Rangasamy [c], Ranjit Mohan Anjana [a], Shiny Abhijit [a], Kuppan Gokulakrishnan [a], Arup Das [b], Viswanathan Mohan [a], Muthuswamy Balasubramanyam [a,*]

New biomarkers to predict Young Onset of Diabetic Retinopathy: Madras Diabetes Research Foundation Research

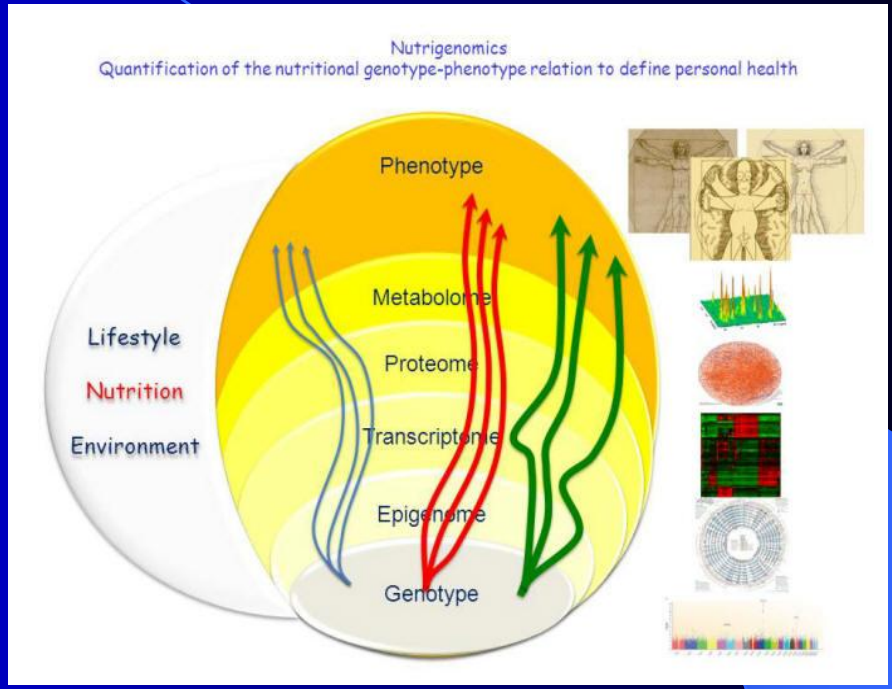
"Type 2 diabetes in younger adults represents an extreme phenotype with a paradoxically increasing trend in Asian Indians and these individuals are highly prone to the development of diabetic microvascular complications like diabetic retinopathy" — says lead authors Muthuswamy Balasubramanyam & Viswanathan Mohan. This means 'earlier the onset of diabetes, faster and greater will be the vision problem'.

"It appears that higher levels of MCP-1 and cathepsin-D in young onset type 2 diabetes patients represent an accelerated aging phenotype — a driving force for faster development of diabetic retinopathy. It is expected that targeting the pathways related to these biomarkers could be a future strategy for preventing the heightened risk of developing diabetic retinopathy in young-onset diabetic patients" — concludes Balasubramanyam.

NUTRIGENOMICS
for Disease Prevention and Intervention



Dietary components can influence not only the inherent qualities of cells, but also the way cells respond to drugs and other treatment interventions.



COMMENTARY

Metformin: Nature's Gift that Keeps on Giving More!

M. Balasubramanyam

Why don't we look for a Metformin equivalent(s) in our Ayurvedic Herbals?

EXPOSOMICS

Exposomics

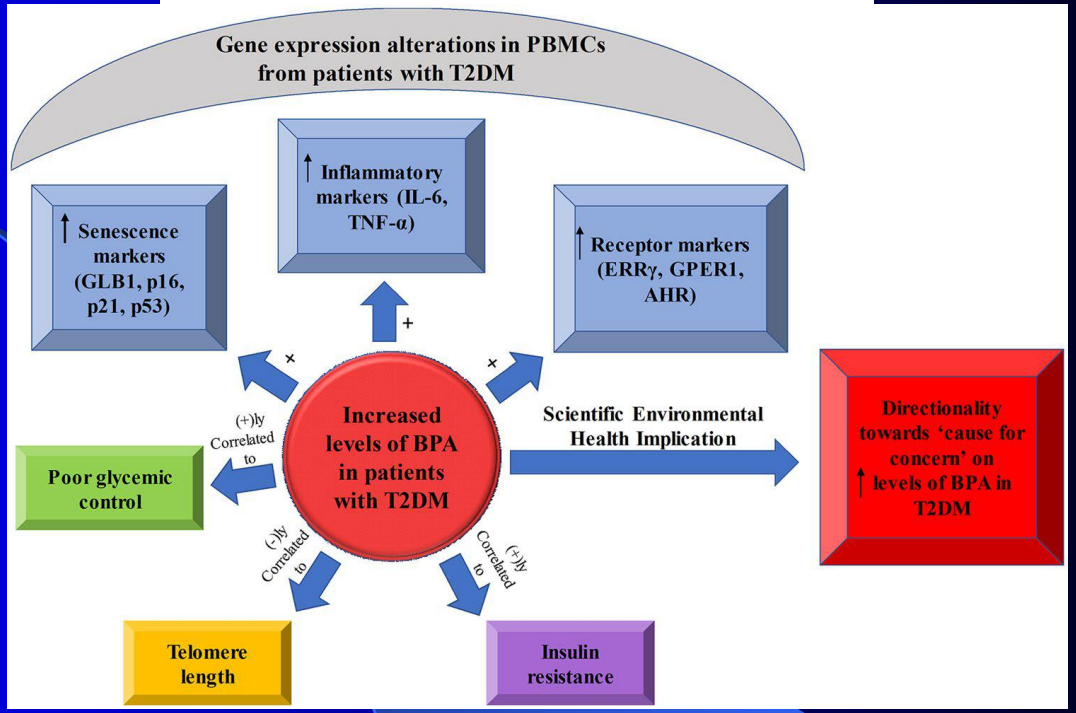
"At it's most complete, the exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards..."

-- Christopher Paul Wild

Molecular and Cellular Biochemistry
https://doi.org/10.1007/s11010-019-03540-9

Novel insights of elevated systemic levels of bisphenol-A (BPA) linked to poor glycemic control, accelerated cellular senescence and insulin resistance in patients with type 2 diabetes

Avinash Soundararajan[1,2] · Paramasivam Prabu[1] · Viswanathan Mohan[1] · Yann Gibert[2,3] · Muthuswamy Balasubramanyam[1]



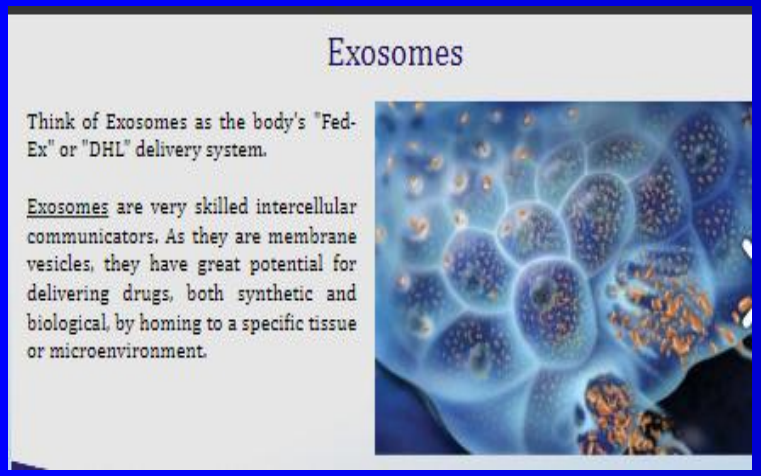
Gerona et al. Environmental Health
DOI 10.1186/s12940-016-0131-2
Environmental Health
RESEARCH Open Access

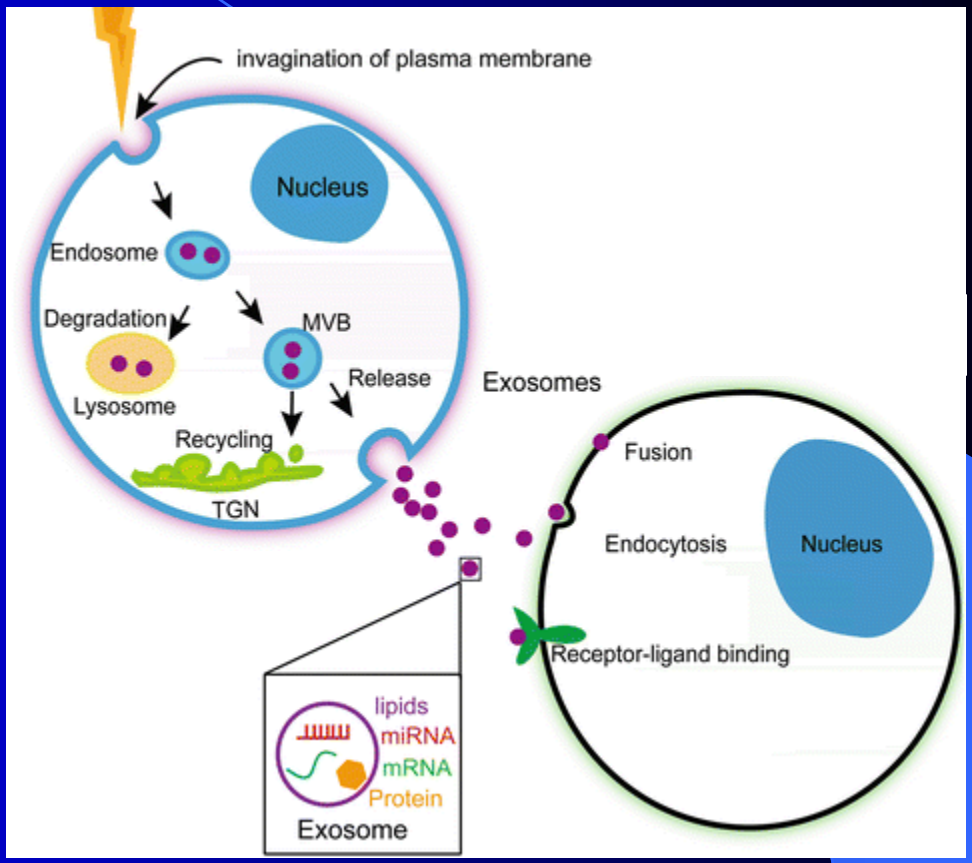
Direct measurement of Bisphenol A (BPA), BPA glucuronide and BPA sulfate in a diverse and low-income population of pregnant women reveals high exposure, with potential implications for previous exposure estimates: a cross-sectional study

Roy R. Gerona[1], Janet Pan[1], Ami R. Zota[1,2], Jackie M. Schwartz[1], Matthew Friesen[1], Julia A. Taylor[4], Patricia A. Hunt[3] and Tracey J. Woodruff[1*]

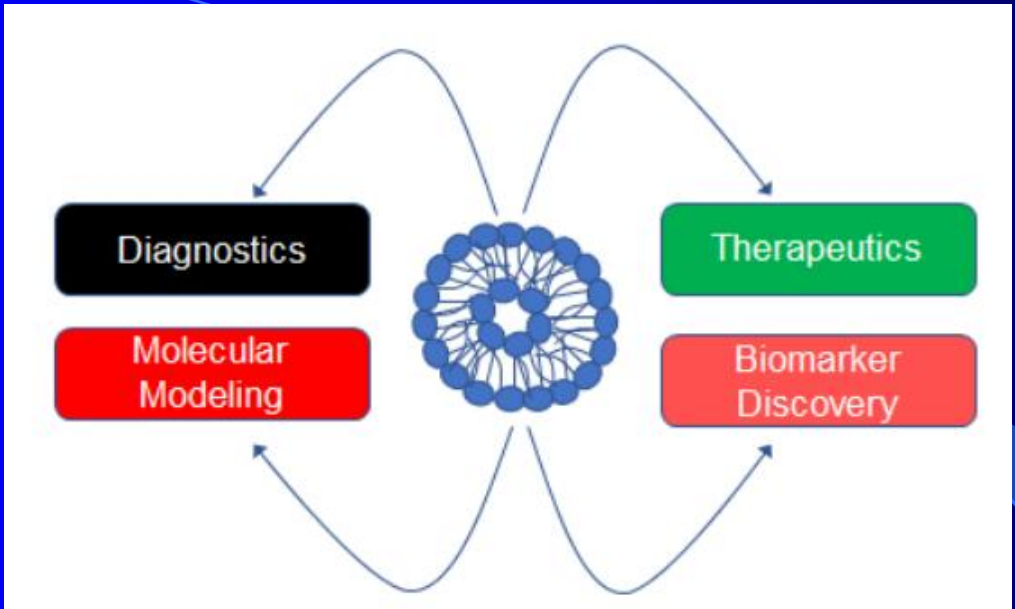
“Evs / EXOSOMES are kind of like FedEx packages”

“Each Exosome carries a tiny cellular cargo and has its own ‘ZIP code,’ which directs it to a particular part of the body.”





Exosomes are programmed to GUIDE, SUPERVISE & MENTOR



Ali et al 2023; Biology

EVs derived from plasma or urine samples contain important molecules that could be used in the diagnostics of various diseases and in some cases reveal information about different stages of disease

Engineered EVs can be loaded or fused with small-molecule drugs and used as a vehicle for targeted delivery and combination drug therapy

The molecules enriched in EVs can be subject to bioinformatic studies and used for computational or molecular modeling

Most importantly, EVs are a rich source of biomarkers in physiology and pathophysiology.

The rationale for investigating the biomarker role of urinary EV miRNAs to predict Diabetic Nephropathy

Diabetes is a leading cause of chronic kidney disease worldwide, and accounts for 30–40% of end-stage renal disease cases in India

While longstanding type 2 diabetes mellitus (T2DM) and poor glycaemic control are risk factors for diabetic nephropathy (DN), South Asian ethnicity has also been linked to a relatively greater susceptibility to this complication; in fact, there are significant differences in the epidemiology of microvascular complications between South Asians and people of other race.

Hyperglycaemia, hypertension and genetic predisposition are among the significant risk factors that affect kidney glomeruli, arterioles, tubules and interstitium.

Micro-albuminuria (MIC) is considered the gold standard indicator of DN, yet it poses certain specificity and sensitivity concerns. Its predictive powers are limited, as structural changes in the glomerular basement membrane and renal vasculature may appear before the onset of MIC. Moreover, clinical factors unrelated to DN can affect MIC status and, recently, it was observed that 30% of DN cases can arise in the absence of obvious MIC.

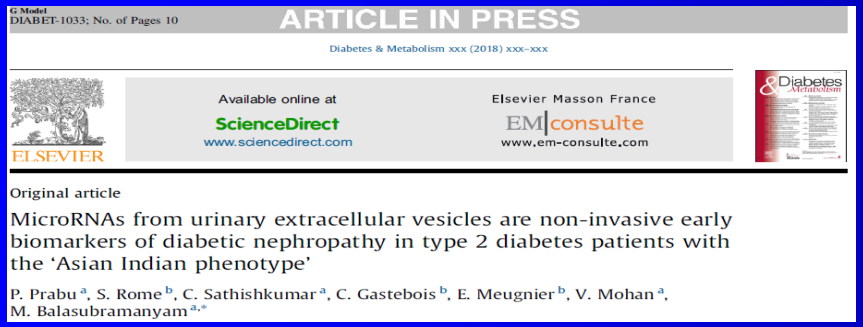
Therefore, there is an unmet clinical need to identify novel, reliable biomarkers reflecting early-stage DN and progressive renal dysfunction in diabetes patients to allow for appropriate therapy that might prevent or slow DN evolution.

Key Findings

A total of 73 miRNAs detected in urinary EVs (NGT) were predicted to target important functions for kidney homoeostasis, thereby validating their use as indicators of kidney dysfunction.

A specific urinary EV miRNA panel comprising of increased levels of let-7i-3p, miR-24-3p and miR-27b-3p, and decreased levels of miR-15b-5p, was found to identify patients with MIC.

ROC curve analysis confirmed this ability to identify MIC in normo-albuminuria T2DM (T2DM-NA) patients and to differentiate between MAC and T2DM patients.
These miRNAs were also predicted to target protein networks involved in the Wnt/b-catenin signalling cascade, activin receptor signalling and cell differentiation/proliferation, and correlated with eGFR, HbA1c, serum creatinine, urea, albumin and blood pressure.



G Model
DIABET-1033; No. of Pages 10
ARTICLE IN PRESS
Diabetes & Metabolism xxx (2018) xxx–xxx

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Original article

MicroRNAs from urinary extracellular vesicles are non-invasive early biomarkers of diabetic nephropathy in type 2 diabetes patients with the 'Asian Indian phenotype'

P. Prabu [a], S. Rome [b], C. Sathishkumar [a], C. Gastebois [b], E. Meugnier [b], V. Mohan [a], M. Balasubramanyam [a,*]

Considering the limitations of MIC test (a gold-standard for predicting DN), our study endorses the utility of urinary miRNAs from EVs as non-invasive 'liquid biopsies' to stratify patients at risk of developing macroalbuminuria (MAC) and diabetic kidney disease.

Beyond research asia RESEARCH NEWS

asia RESEARCH NEWS

Medicine News

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Article Released Fri-26th-October-2018 09:06 GMT

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"Liquid-Biopsy" microRNA biomarkers to predict risk for diabetic kidney disease

A recent study from the Madras Diabetes Research Foundation, Chennai, India & University of Lyon, France – brings a new hope for using 'liquid-biopsy' exosomal microRNA biomarkers (miRNAs) from urine to predict risk for kidney disease in diabetes patients.

Patient data and computing tools are the pre-requisites for a quality data outcomes of Omics advancements. Well in advance, US has made substantial investment in Health information technology & Big Data analysis in relation to drug discovery. This is slowly catching up in India…Healthcare Technology Innovation Centre in IIT-M and other such initiatives in the rest of the country.

.

US has made substantial investment in health information technology (HIT)

Health Information Technology for Economic and Clinical Health (HITECH) Act of the American Recovery and Reinvestment Act (ARRA) (Blumenthal, 2011)

- Incentives for electronic health record (EHR) adoption by physicians and hospitals (up to $27B)
- Direct grants administered by federal agencies ($2B, including funding for health information exchange, workforce development, etc.

OREGON HEALTH & SCIENCE UNIVERSITY

- Biomedical Informatics educational program
- Big Data to Knowledge (BD2K) projects
- Informatics Discovery Lab (IDL)

Healthcare Technology Innovation Centre

collaborate ▸ innovate ▸ impact

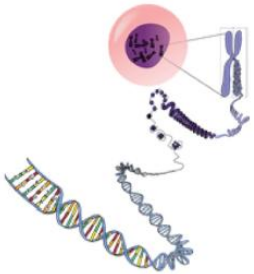
A joint initiative of

Indian Institute of Technology Madras

Department of Biotechnology, Ministry of Science and Technology

Biomedical Big Data

Electronic Health Records



-Omic Data

-Omic and Electronic Health Records Big Data Analytics for Precision Medicine

Lancet Diabetes Endocrinol 2018

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Interpretation We stratified patients into five subgroups with differing disease progression and risk of diabetic complications. This new substratification might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

Precision medicine in diabetes

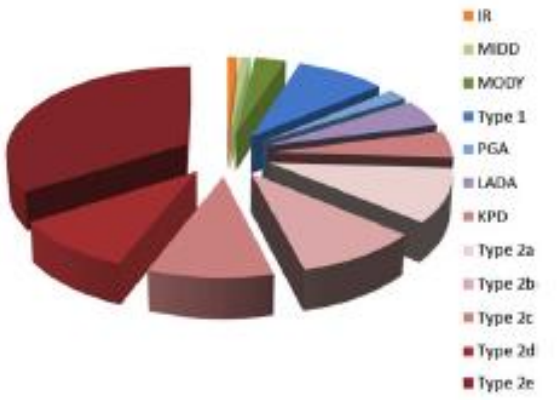


Figure 1. Heterogeneity of diabetes. The pie chart represents the multiple ways people can develop hyperglycemia and reach the diagnosis of diabetes. The size of each piece only represents an approximate proportion of prevalence in the population. IR, rare genetic forms of insulin resistance: MIDD, maternally inherited diabetes and deafness: MODY, maturity-onset diabetes of the young: type 1, type 1 diabetes: PGA, diabetes caused in the setting of polyglandular autoimmune syndromes: LADA, latent autoimmune diabetes of adults: KPD, ketosis-prone diabetes: type 2a–2e, hypothetical subgroups of type 2 diabetes.

Integrative Analysis of Multimodal -Omic Data

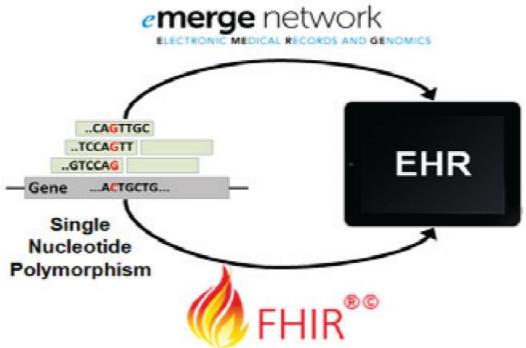
Genomics
Transcriptomics
Epigenomics

→ Novel Discovery of Cancer Subtypes ←

Proteomics
Metabolomics

Fast Healthcare Interoperability Resources (FHIR)

Integrating -Omic Knowledge into the EHR System



Severe auto-immune diabetes (SAID)
Severe insulin-deficient diabetes (SIDD)
Severe insulin-resistant diabetes (SIRD)
Mild obesity-related diabetes (MOD)
Mild age-related diabetes (MARD)

BMJ Open Diabetes Research & Care

Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study

Anjana et al 2020

Significance of this study

What is already known about this subject?

- Recently five distinct 'clusters' of individuals with diabetes with significantly different characteristics have been identified in a Scandinavian population.
- The unique Asian Indian phenotype predisposes them to young-onset type 2 diabetes (T2D).

What are the new findings?

- For the first time in India (and South Asia), clustering was done on 19 084 individuals with T2D using eight clinically relevant variables (age at diagnosis, body mass index, waist circumference, glycated hemoglobin, triglycerides, high-density lipoprotein cholesterol, and C peptide fasting and stimulated).
- Four replicable clusters were identified, two of which were unique to the Asian Indian population.
- The novel cluster 'Combined Insulin Resistant and Deficient Diabetes' is of particular importance as it is characterized by difficult-to-control hyperglycemia and increased hazards of kidney disease and retinopathy.

Cluster 1 (Severe Insulin Deficient Diabetes, SIDD), Cluster 2 (Insulin Resistant Obese Diabetes, IROD), Cluster 3 (Combined Insulin Resistant and Deficient Diabetes, CIRDD) and Cluster 4 (Mild Age-Related Diabetes, MARD). While SIDD and MARD are similar to clusters reported in other populations, IROD and CIRDD are novel clusters. Cox proportional hazards showed that SIDD had the highest hazards for developing retinopathy, followed by CIRDD, while CIRDD had the highest hazards for kidney disease

Expanding Etiology on Novel Subtypes of Type 2 Diabetes

Distinct Molecular Signatures of Clinical Clusters in People With Type 2 Diabetes: An IMI-RHAPSODY Study

Slieker et al, Diabetes Volume 70,

Genome-wide association analyses highlight etiological differences underlying newly defined subtypes of diabetes

Aly et al. Nature Genetics, November

Diabetes Care. 2022 May 24;dc212489. doi: 10.2337/dc21-2489. Online ahead of print.

Novel Subgroups of Type 2 Diabetes Display Different Epigenetic Patterns, Which Associate With Future Diabetic Complications

International Journal of *Molecular Sciences*

Sulaiman et al 2025

Article

Characterizing Circulating microRNA Signatures of Type 2 Diabetes Subtypes

Cell Reports Medicine

Data-driven subgroups of prediabetes and the associations with outcomes in Chinese adults

Exploratory Research and Hypothesis in Medicine **2023** vol. 000(000) | 000–000 Epub
DOI: 10.14218/ERHM.2023.00028

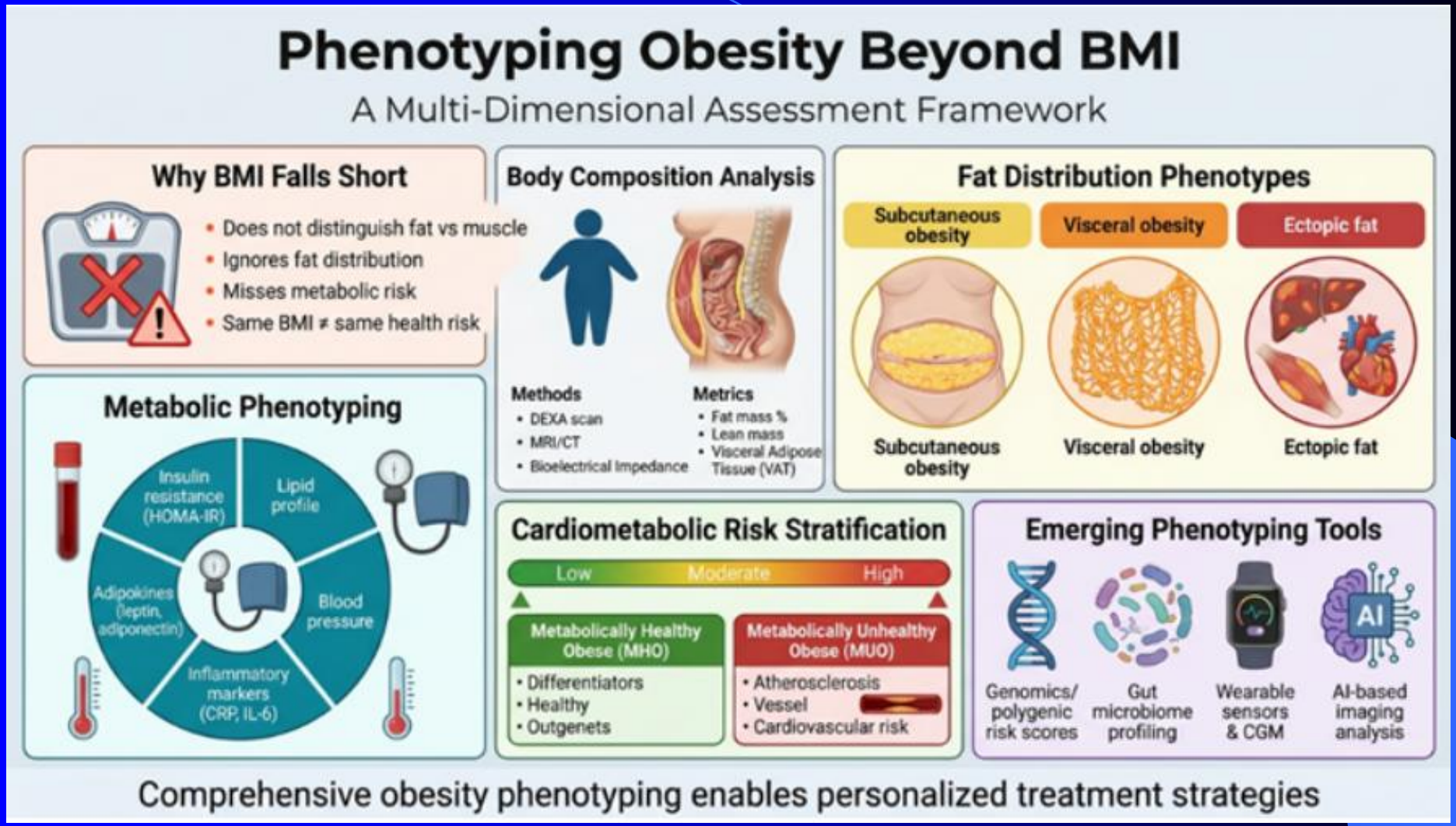
Editorial

Type 2 Diabetes: Is it Time to Target β-cell Heterogeneity?

Muthuswamy Balasubramanyam*

Department of Cell and Molecular Biology, Madras Diabetes Research Foundation, Chennai, India

Chakaroun et al; Nature Medicine 2026

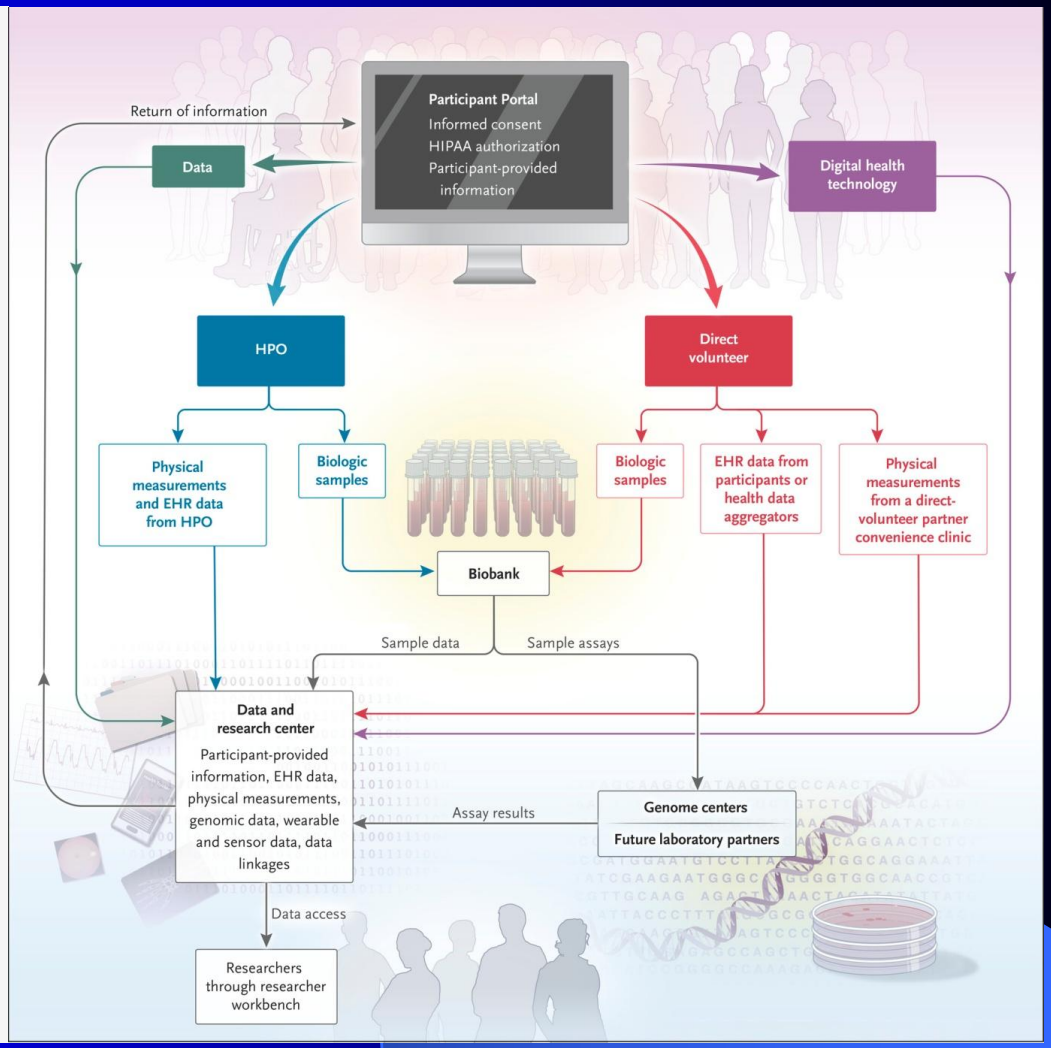


All of US is a major program in USA – building a research program of 1,000,000 + people on Holistic Clinical Research, Omics Findings and Data Science with a goal of Precision Medicine.

All of Us RESEARCH PROGRAM

The future of health begins with you

The *All of Us* Research Program is a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health. By taking into account individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine.



All of Us RESEARCH PROGRAM

All of US research program is a role model attempt for many other nations and it is already yielding good results of clinical utility in a variety of disease-states.

NIH's *All of Us* Research Program Awards $1.5 Million to Institutions Collaborating with Tribal Communities to Advance Precision Medicine

Utilizing the *All of Us* Research Program for Substance Use and Mental Health Research

Research Roundup: *All of Us* Participants' Fitbit Data Drive New Research

All of Us Research Program Updates Data Use Eligibility to Propel Precision Medicine

NIH launches largest precision nutrition research effort of its kind

All of Us Research Program Starts Collecting New Mental Health and Well-Being Data

All of Us Research Program Seeks Input on Environmental Health Data

All of Us Research Program Makes Nearly 250,000 Whole Genome Sequences Available to Advance Precision Medicine

All of Us Data Teaches Us About Who Gets Vaccinated

Discovering More Genetic Variants Thanks to *All of Us* Data

What *All of Us* Data Says About Blindness and Mental Health During COVID-19

Learning More About Dementia Risk Through *All of Us*

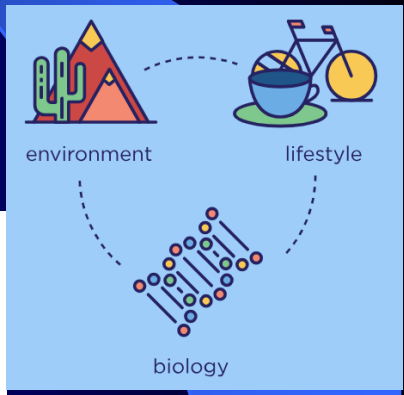
All of Us Data Clarifies What We Know About Hispanic Heart Health

Steps to Better Health With *All of Us*

Study Links Birthplace and Cancer Risk Among Hispanic *All of Us* Participants

All of Us Data Helps Better Predict Hospital Readmission for Patients With Sepsis

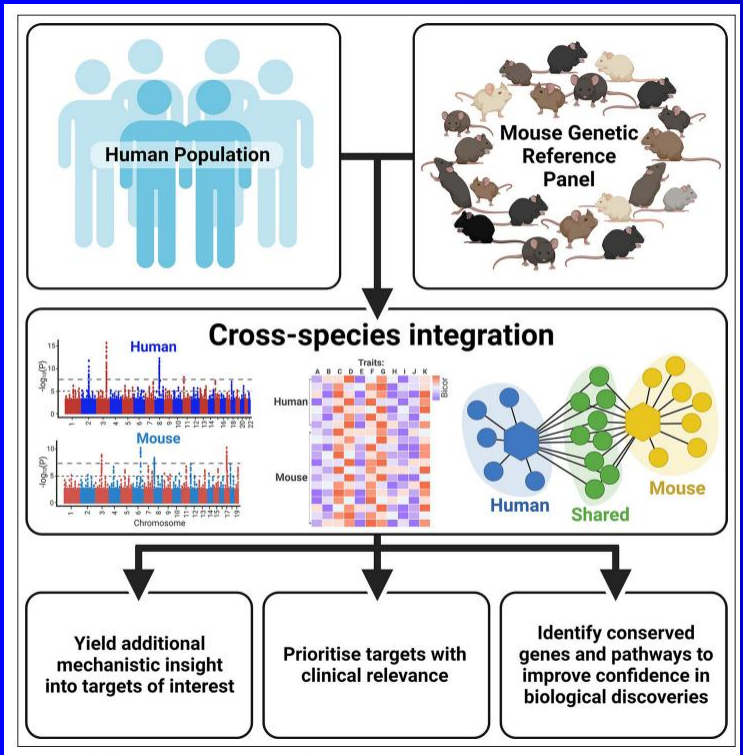
All of Us Meets FDA Standards to Deliver DNA Research Results to Participants



The potential of integrating human and mouse discovery platforms to advance our understanding of cardiometabolic diseases

Aaron W Jurrjens[1,2], Marcus M Seldin[3], Corey Giles[1,4,5], Peter J Meikle[1,2,4,5], Brian G Drew[1,2,4*†], Anna C Calkin[1,2,4*†]

Key advantages and challenges of integrating complementary genetic and multi-omics data from human and mouse populations to advance biological discovery



Role of Epigenetics and Metabolomics in Predicting Endothelial Dysfunction in Type 2 Diabetes

An evaluation of the National Institutes of Health grants portfolio: identifying opportunities and challenges for multi-omics research that leverage metabolomics data

Consensus Statement https://doi.org/10.1038/s41591-023-02502-5

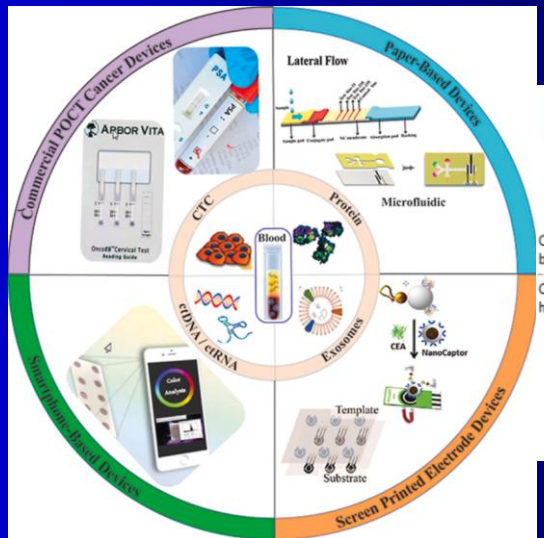
Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine

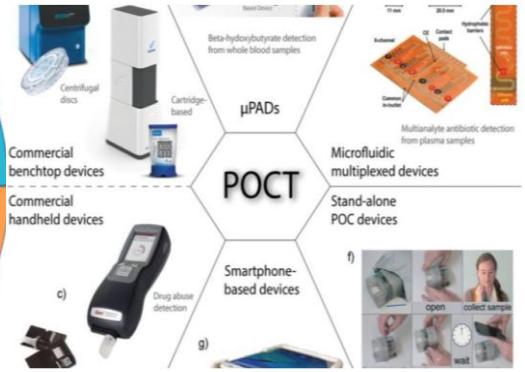
Applications of Machine Learning Models With Medical Images and Omics Technologies in Diabetes Detection

Article https://doi.org/10.1038/s41587-022-01520-x

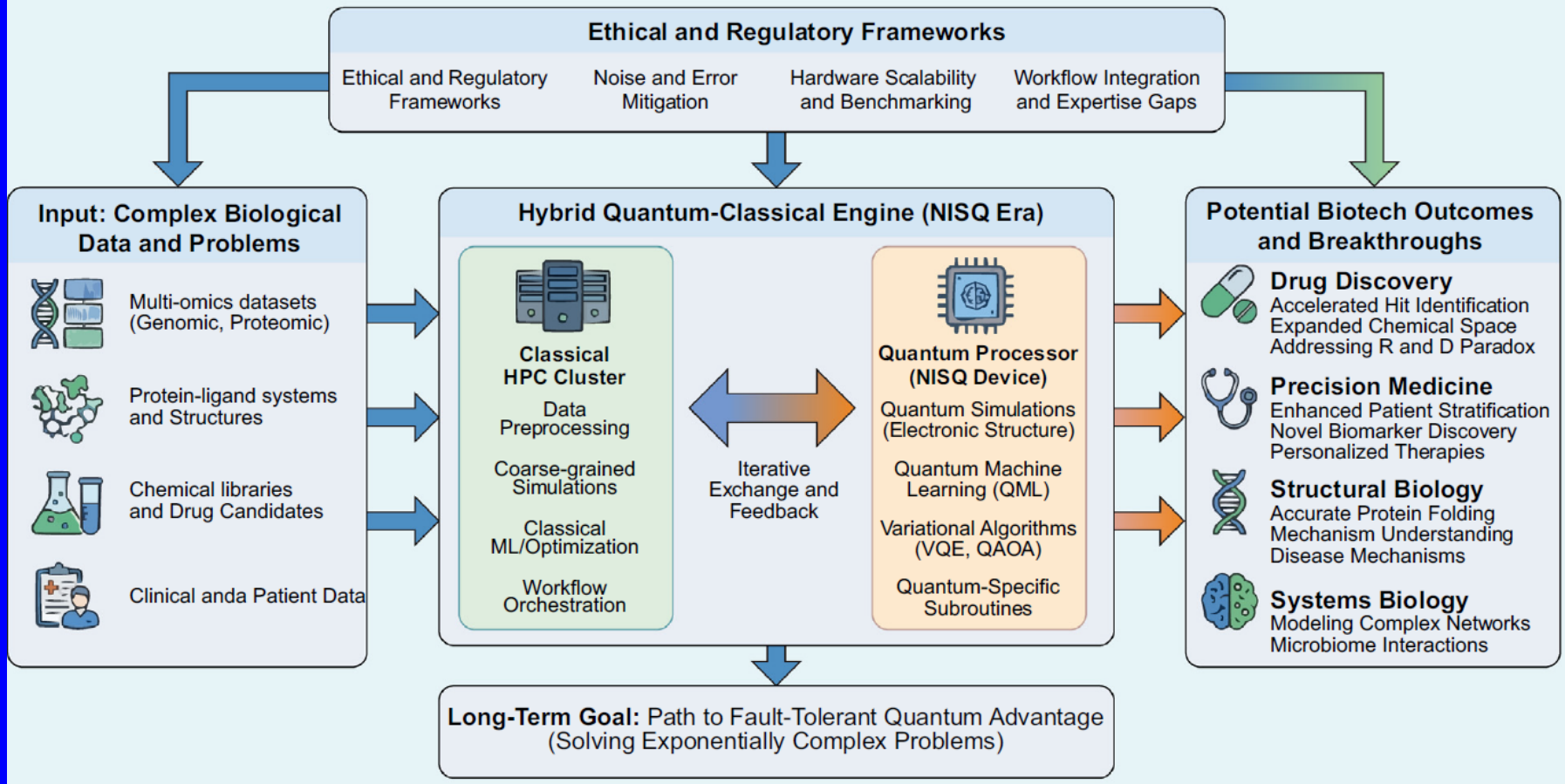
Discovery of drug–omics associations in type 2 diabetes with generative deep-learning models

Evolution of Point-of-Care (POC) Devices

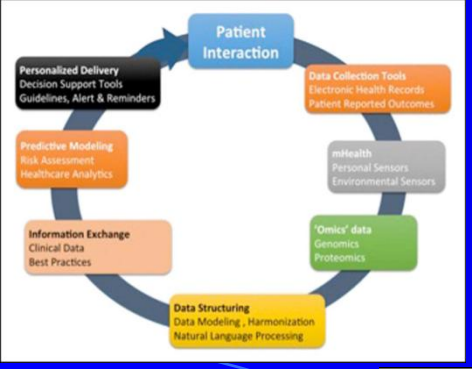




Hybrid Quantum-Classical Workflow in the NISQ Era: Catalyzing Biomedical Innovation

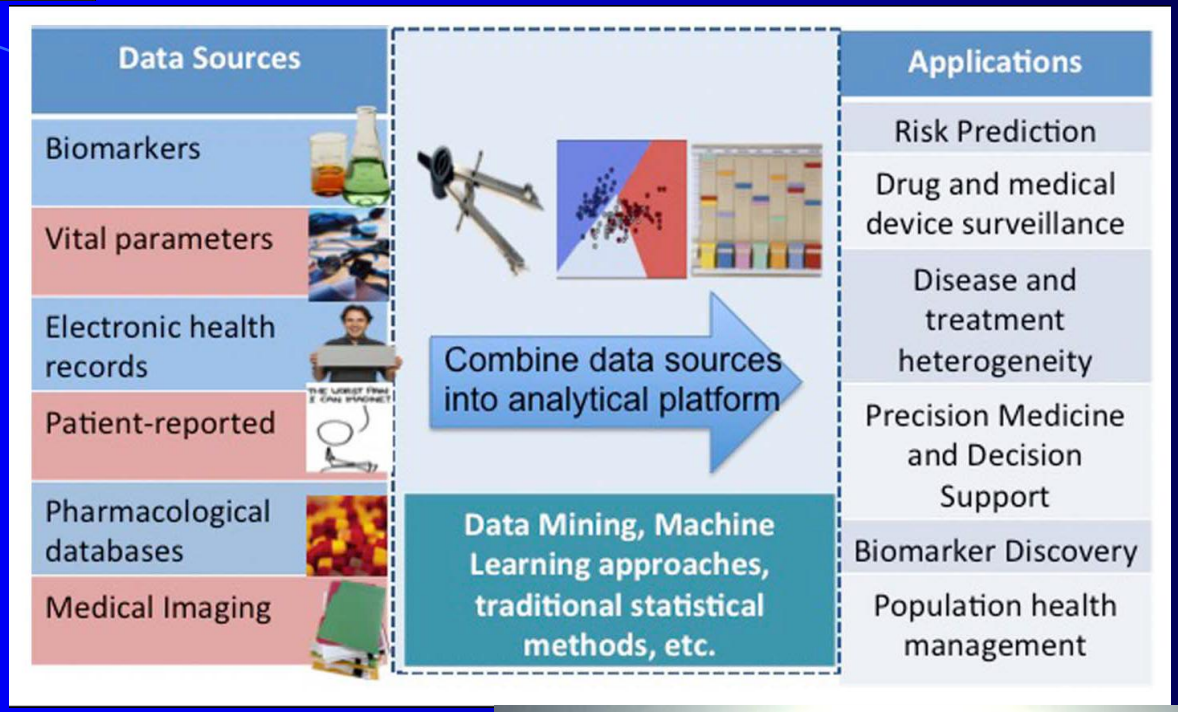


Trends in Biotechnology



- It appears that Multidisciplinary Research
- with Big Data is the future of medicine.

Big Dreams With Big Data!



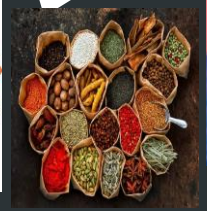
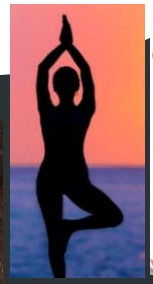
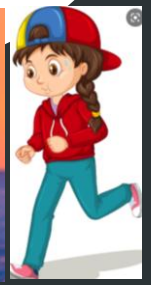
Medicine has been a clinical science, supported by data.

Medicine is about to become a data science, supported by clinicians.

Hi…. It is not so easy now!
Once Lab reports are ready, it will go to the Doctor's room; Then
Doctor needs to talk to Doctorates!:
System-Biologists, Bioinformaticians, Algorithm makers; The so-called DATA Scientists…
Then IT Future of Medicine combined with Machine Learning & Artificial Intelligence – Then only, Clinical Decision Making
and finally Prescription!!!!!!

Precision Medicine

Consult me too!
I too have a big SAY in Precision Medicine……

I am waiting for you at the airport.
You said lab reports are ready; just to see the doctor and get prescription

Thanks to

Funding Agencies &

My Disease-Biology Team

THANK YOU