The Complexity of Patients with Diabetes: Research & Development Opportunities from the Perspective of Patient Needs and Challenges

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Person 1

- 65 year old Chinese Male
- Strong family history of T2DM
- T2DM since 50 years old
- Hypertension
- Ex-smoker
- PO Glipizide 10mg BD
- PO Metformin 850mg BD
- HbA1c 7.5%, Creatinine 100 umol/L, eGFR 58
- Urine microalbumin +ve, Early DM retinopathy

Person 2

- 44 Chinese Male
- Married with 2 kids – 4 and 1+ years
- **T2DM diagnosed 5 years ago**
- HbA1c 12.5% when admitted for Nephrotic Syndrome 6 months ago
- Urine Protein > 4g/day, Serum Albumin 24
- Creatinine 110, eGFR >60
- Proliferative retinopathy with maculopathy
- Ischaemic dilated cardiomyopathy, Angiogram(-)
- **Father had T2DM and ESRF, IHD**

Person 3

- 38 Chinese Female
- Simple mind, Obesity – BMI 33 kg/m^2
- T2DM since 23 years old
- Her mother has psychiatric illness
- Sister supervises her care as best she can
- **Average HbA1c 11%** (Range 5.8 – 13.0%)
- Normotensive
- **No urine albumin, eGFR > 60, Creatinine 50**
- Metformin, Sulphonylurea, Basal Insulin

Person 4

- 36 year old Chinese Male
- **Known T1DM** since 24 years old
- Chronic Lymphocytic Thyroiditis
  (aka Hashimoto's)
- Long acting insulin analogue 20 units OM
- Regular insulin 8 units TDS premeals
- HbA1c 8.2% March 2009
- Canoe Instructor / Water Sports

HAAF

(hypoglycemia-associated autonomic failure)

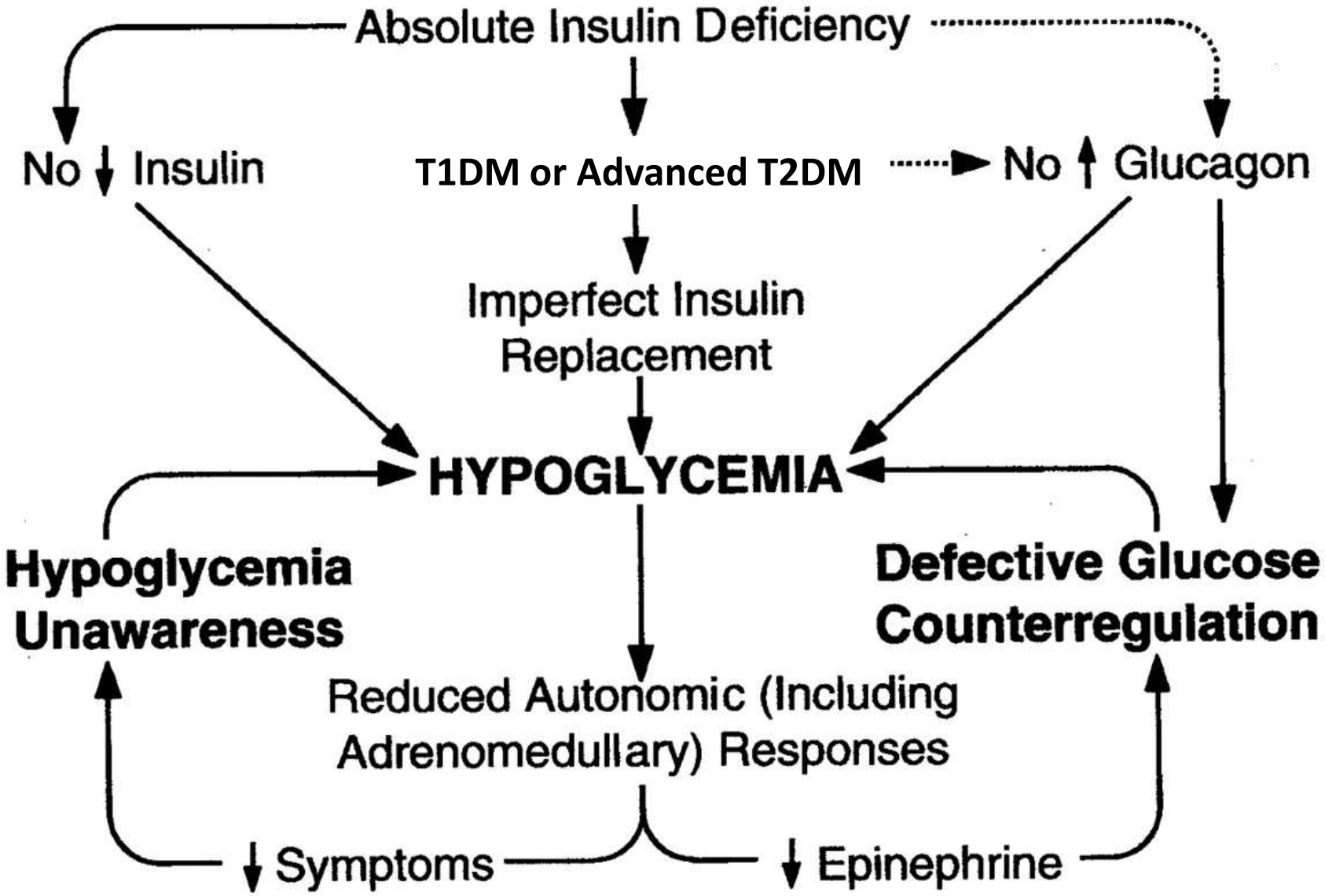
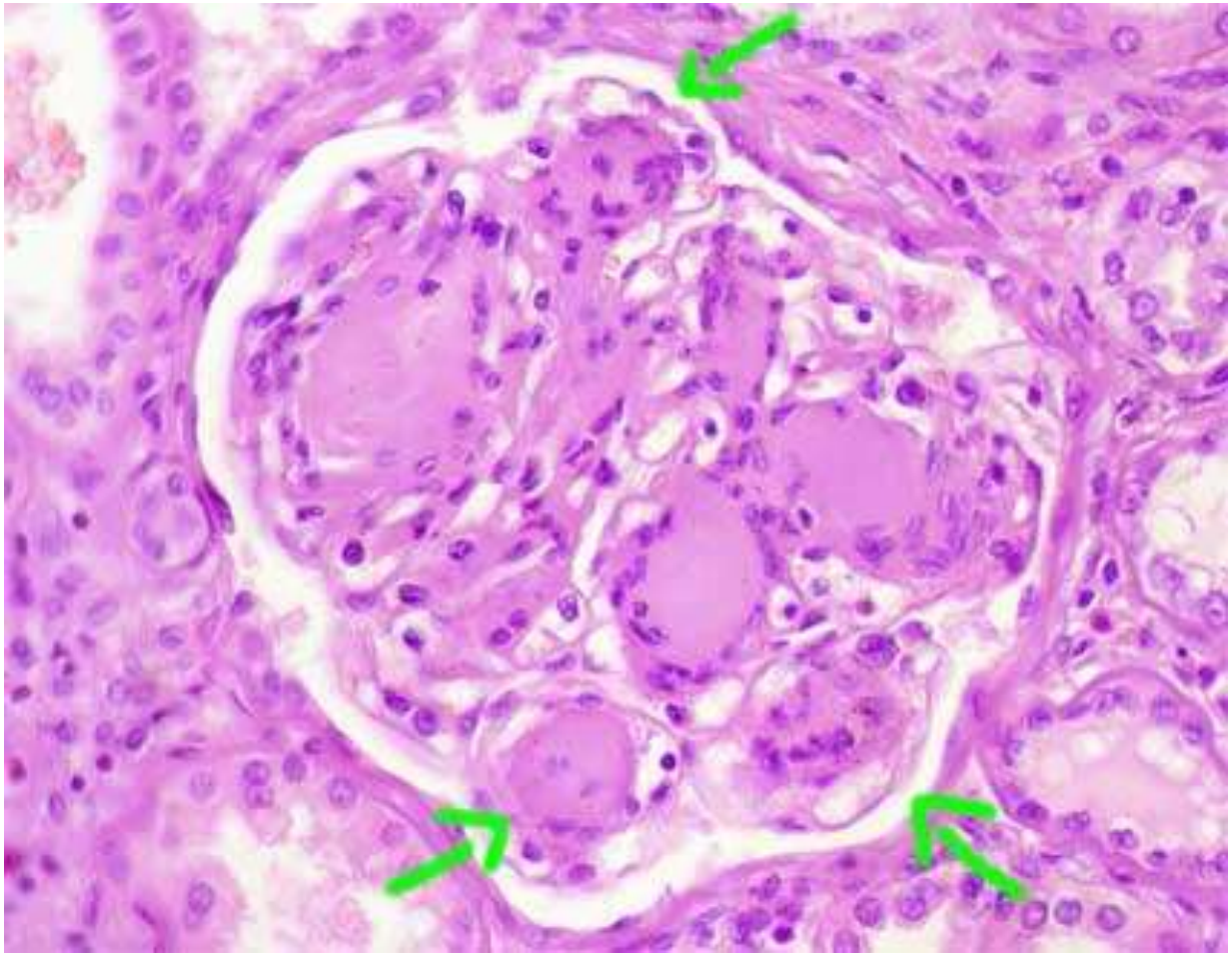


Table 3. Initial Treatments for Various Diabetes Subtypes.*

Diabetes Subtype	Causal Genes	Optimal Treatment
Type 1 diabetes	About 40 known (genes in HLA region, *INS*, *PTPN22*, and others)	Lifelong insulin
Type 2 diabetes	About 40 known (*TCF7L2*, *CDKAL1*, and others)	Metformin as primary treatment; also sulfonylureas, glitazones, or insulin
LADA	Genes in HLA region, *INS*, and *PTPN22* (as in type 1 diabetes)	Early recourse to insulin therapy
GCK-MODY	*GCK*	Diet modification
HNF1A MODY	*HNF1A*	Sulfonylureas (low dose)
Mitochondrial diabetes	*MTTL1*	Early recourse to insulin therapy
Lipodystrophies	*LMNA*, *PPARG*, *AGPAT2*, *CAV1*, *BSCL2*, *LMNB2*, and *AKT2*	Uncertain; thiazolidinediones for some subtypes
Neonatal diabetes	*KCNJ11*, *ABCC8*	Sulfonylureas (high dose)
Neonatal diabetes	*INS*	Insulin

* GCK denotes glucokinase, LADA latent autoimmune diabetes in adults, MODY maturity-onset diabetes of the young, and tRNA transfer RNA.

DM Nephropathy



DM Nephropathy

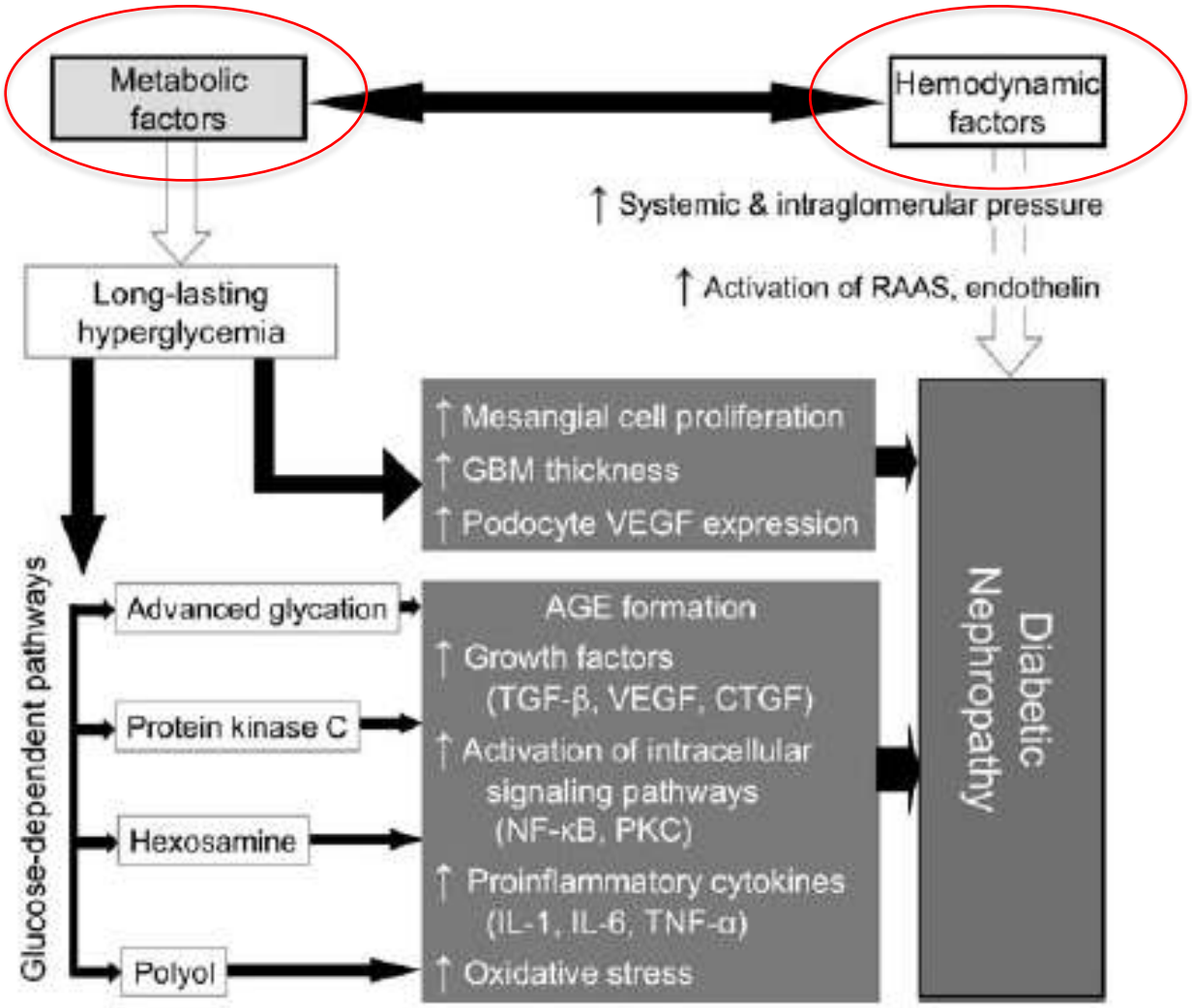
- Diabetic nephropathy is the leading cause of end stage renal disease (ESRD) worldwide
- Glycemic control and Blood pressure and are the two most important factors predicting the progression of diabetic nephropathy
- Genetic predisposition:
  - Pedigree studies show familial aggregation in both T1DM and T2DM
  - Difference prevalence among various ethnic groups
- The likelihood of developing overt proteinuria was 14%, 23% and 46% in patients with none, one or both parents with proteinuria

* Shaw, et.al. Diabetes Res Clin Pract 2010; 87: 4-14

TABLE 1. Management of diabetic nephropathy by stage of renal function

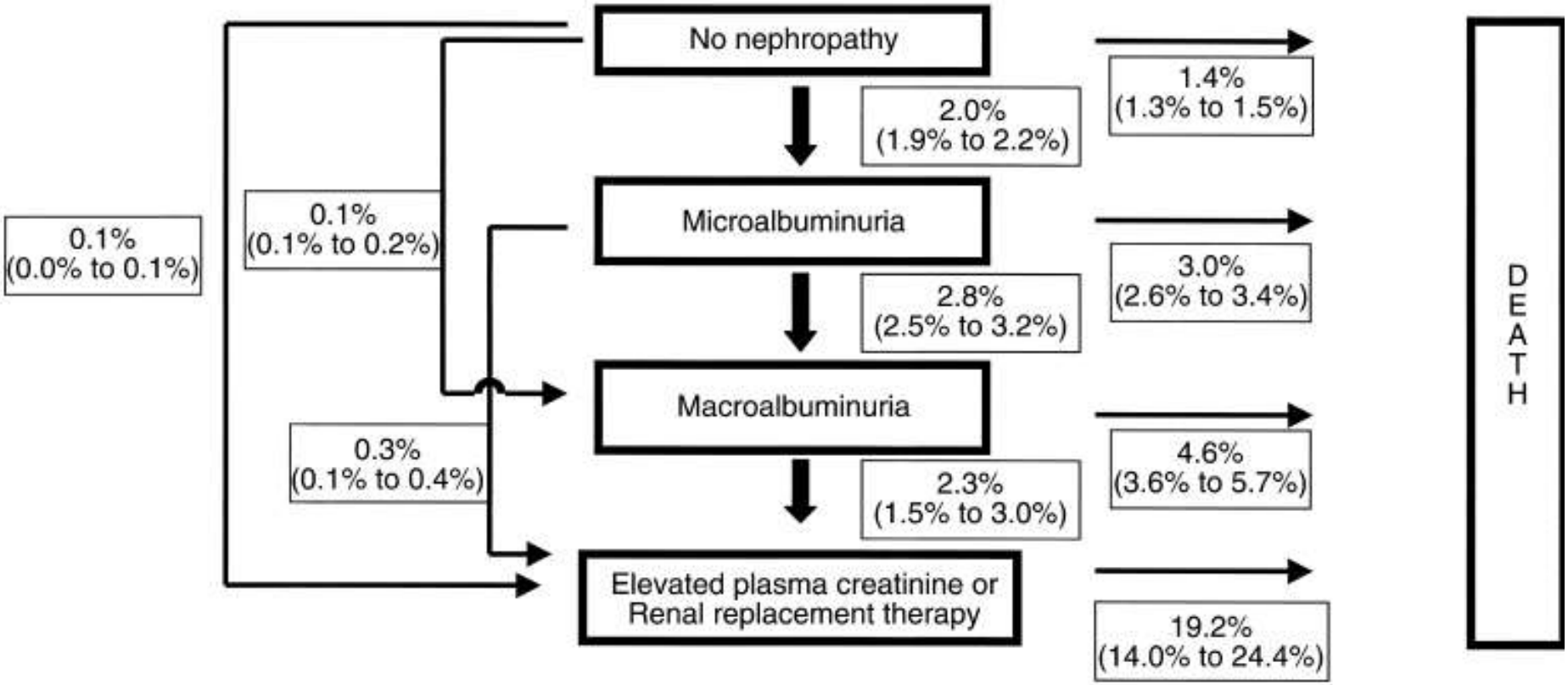
Stage	Description	GFR (ml/min per 1.73 m^2 body surface area)	Management recommendations	Drug regimens
1	Kidney damage with normal or mildly increased GFR	≥90	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl	Add ACE/ARB if urine microalbumin ≥30 mg/g creatinine
2	Kidney damage with mildly decreased GFR	60–89	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl	ACE/ARB recommended for all patients
3	Moderately decreased GFR	30–59	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl Refer patients not meeting treatment goals to nephrology for preparation of impending renal failure Monitor for anemia Monitor for secondary hyperparathyroidism	ACE/ARB recommended for all patients Discontinue metformin, all sulfonylureas except glipizide, nateglinide, α-glucosidase inhibitors, GLP-1 analogs Reduce doses of dipeptidyl peptidase-4 inhibitors Add erythropoietin if Hgb <9 mg/dl Add calcitriol when 1,25-dihydroxyvitamin D is low or when PTH >2 × upper limits of normal
4	Severely decreased GFR	15–29	A1c goal ~ 7.0% BP goal <130/85 LDL goal <100 mg/dl Refer to nephrology for preparation of impending renal failure and consideration of shunt placement Monitor for anemia Monitor for secondary hyperparathyroidism	ACE/ARB recommended for all patients with careful monitoring of serum K Insulin therapy recommended for most patients with diabetes Add erythropoietin if Hgb <9 mg/dl Add calcitriol when 1,25-dihydroxyvitamin D is low or when PTH >2 × upper limits of normal
5	End-stage renal failure	<15 or dialysis	Dialysis or kidney transplantation	

Incomplete Understanding of Pathogenesis



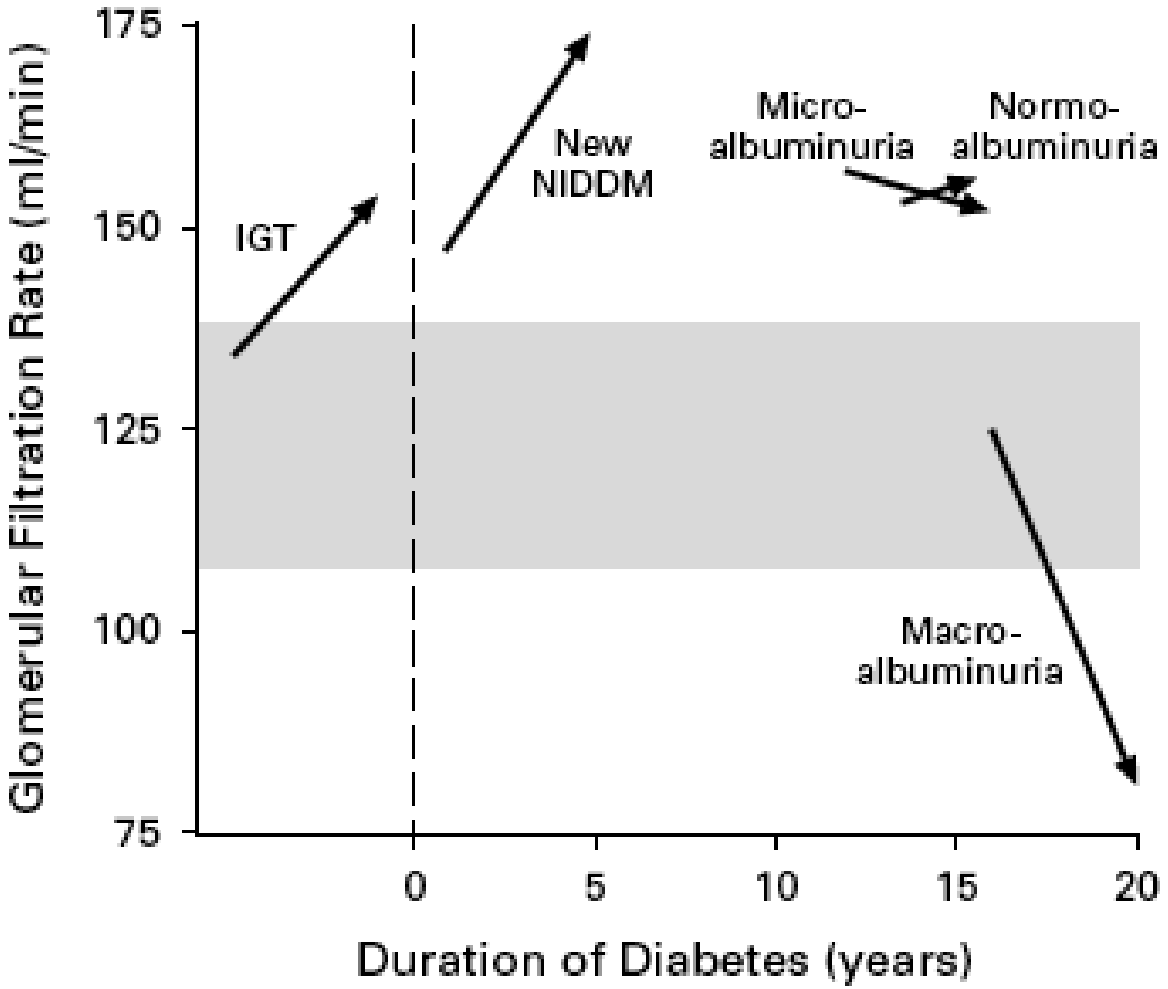
Am J Kidney Dis 2010; 55: 928-940

Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64)



Kidney International, Vol. 63 (2003), pp. 225–232

Clinical Course

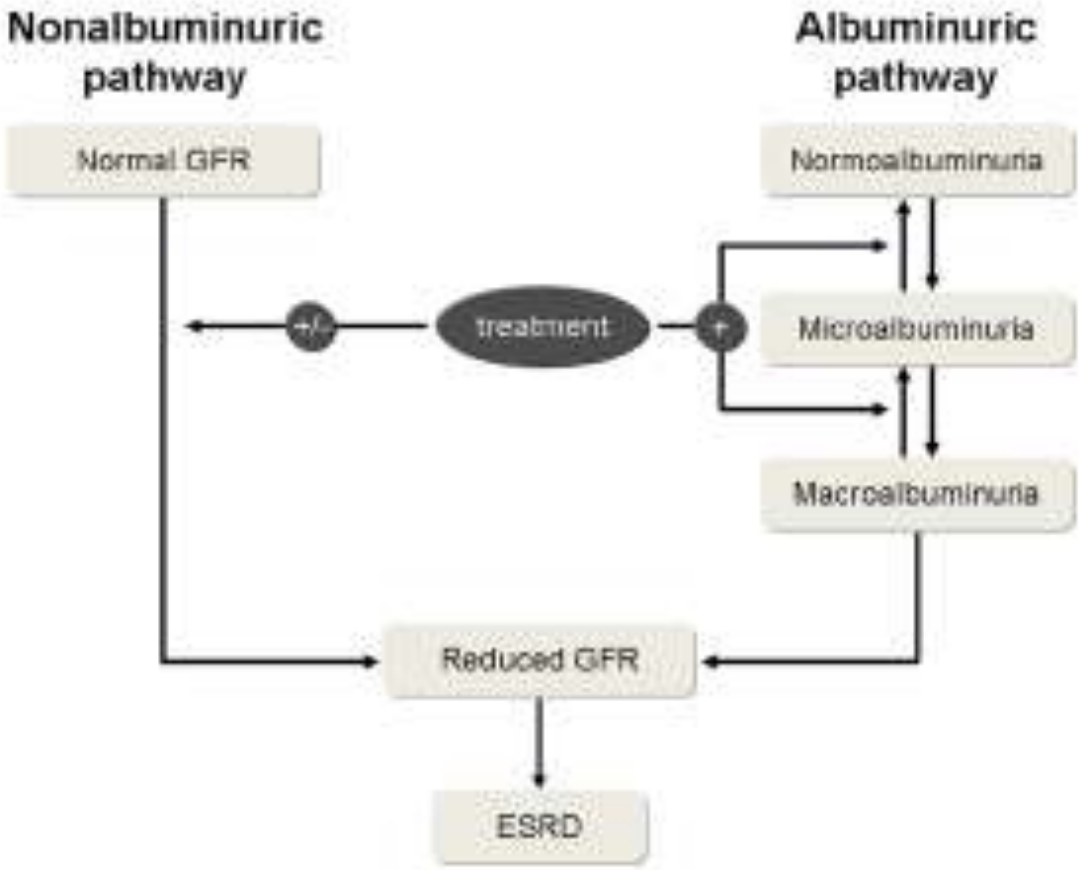


Only approx 30% of patients with microalbuminuria progress to overt DN after 10 years

Renal function decline occur at a rate of 1 ml/min/month in patients with macroalbuminuria

Nelson, RG, et.al. Development and progression of renal disease in Pima Indians with non insulin dependent diabetes mellitus. N Eng J Med 1996; 355: 1636-1642

Diabetic Nephropathy with Normoalbuminuria



Pugliese, G. Updating the Natural History of Diabetic Nephropathy. Acta Diabetol (2014): 51: 905-915

Diabetic Nephropathy with Normoalbuminuria

Table 2 Longitudinal and cross-sectional studies on the prevalence of microalbuminuric renal impairment in patients with type 1 or 2 diabetes

Study, authors (reference)	Diabetes type	Patients with diabetes, *n*	Follow-up, years	Patients with renal impairment*		
				Total, *n* (% of cases)	Nonalbuminuric, *n* (% of total)	With neither albuminuria nor retinopathy, *n* (% of total)
Longitudinal studies						
Molitch et al. [37]	1	1,439	19	89 (6.2)	21 (23.6)	ND
Retnakaran et al. [36]	2	4,006	8	1,132 (28.3)	575 (50.8)	
Cross-sectional studies						
Kramer et al. [33]	2	1,197	NA	171 (14.3)	60 (35.1)	51 (29.8)
MacIsaac et al. [34]	2	301	NA	109 (36.2)	43 (39.4)	32 (29.4)
Dwyer et al. [35]	2	11,573	NA	2,586 (22.3)	1,038 (40.1)	ND
Thomas et al. [38]	2	3,983	NA	920 (23.1)	506 (55.0)	ND
Penno et al. [39]	2	15,773	NA	2,959 (18.8)	1,673 (56.6)	1,280 (43.3)
Rodriguez-Poncelas et al. [40]	2	1,145	NA	206 (18.0)	143 (69.4)	ND
Mottl et al. [41]	2	2,798	NA	575 (20.6)	298 (51.8)	ND
Ninomiya et al. [42]	2	10,640	NA	2,033 (19.1)	1,252 (61.6)	ND
Drury et al. [43]	2	9,795	NA	519 (5.3)	307 (59.2)	ND

Pugliese, G. Updating the Natural History of Diabetic Nephropathy. Acta Diabetol (2014): 51: 905-915

Need for Alternative Biomarkers in DN

Currie G *et al*. Biomarkers in diabetic nephropathy

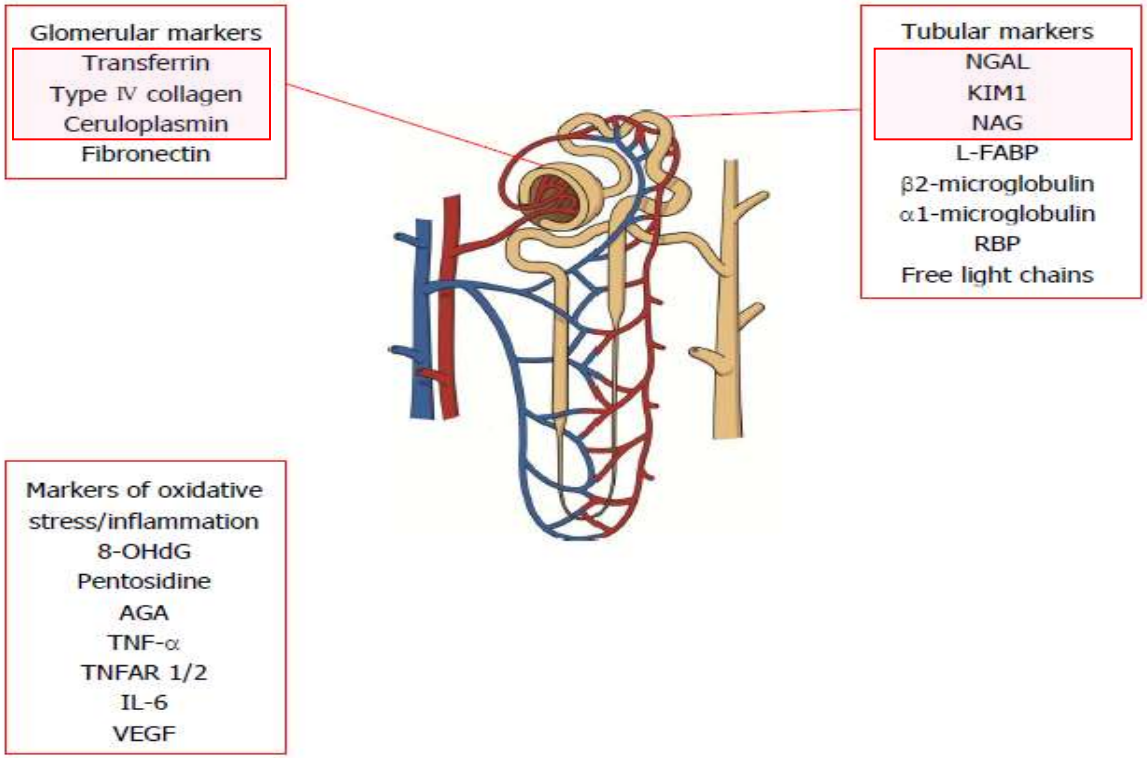


Figure 1 Biomarkers for diabetic nephropathy. NGAL: Neutrophil gelatinase associated lipocalin; KIM1: Kidney injury molecule 1; NAG: N-acetyl-b-d-glucosaminidase; L-FABP: Liver-type fatty acid binding protein; RBP: Retinol binding protein; 8-OHdG: 8-oxo-7,8-dihydro-2'-deoxyguanosine; AGA: α-1-acid glycoprotein; TNFAR 1/2: Tumor necrosis factors-α receptors 1 and 2; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor.

Proteomic eg Panels of Urine Markers: CKD273 urine peptides – 85% sensitive 100% specific

Metabolomic

Genomic Approaches

Table 1 | Major consortia addressing the genetic basis of diabetes complications and associated traits

Acronym	Full name	Trait of Interest	URL
CARDIoGRAM*plus*C4D[133]			ogramplusc4d.org/
CARe consortium[77]			.nih.gov/research/ics-genomics/care
DCCT/EDIC[134]			iddk.nih.gov/dm/pubs/
DIAGRAM[109]	DIAbetes Genetics Replication And Meta-analysis consortium	Type 2 diabetes	http://diagram-consortium.org/about.html
FIND	Family Investigation of Nephropathy and Diabetes	Diabetic kidney disease	https://www.niddkrepository.org/studies/find
GENIE[60]	GEnetics of Nephropathy —an International Effort	Diabetic kidney disease	http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000389.v1.p1
GIANT[135]	The Genetic Investigation of Anthropometric Traits consortium	Anthropometric traits	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium
GoKIND[136]	Genetics of Kidneys in Diabetes study	Diabetic kidney disease	https://www.niddkrepository.org/studies/gokind/
JDRF–DNCRI	Diabetes Research Foundation–Diabetic Nephropathy Collaborative Research Initiative	Diabetic kidney disease	http://jdrf.org/press-releases/jdrf-forms-largest-ever-international-effort-to-research-genetics-of-diabetic-kidney-disease/
MAGIC[137]	The Meta-Analyses of Glucose and Insulin-related traits consortium	Glycaemic traits	http://www.magicinvestigators.org/
SUMMIT[76]	SUrrogate markers for Micro- and Macro-vascular hard endpoints for Innovative diabetes Tools	Complications of diabetes	http://www.imi-summit.eu/

So far…Search for specific variants relatively unrewarding

1) Phenotype imprecision: Albumin/ESRD, ? Mechanistic heterogenecity

2) Inadequate sample size

What causes weight gain and obesity?

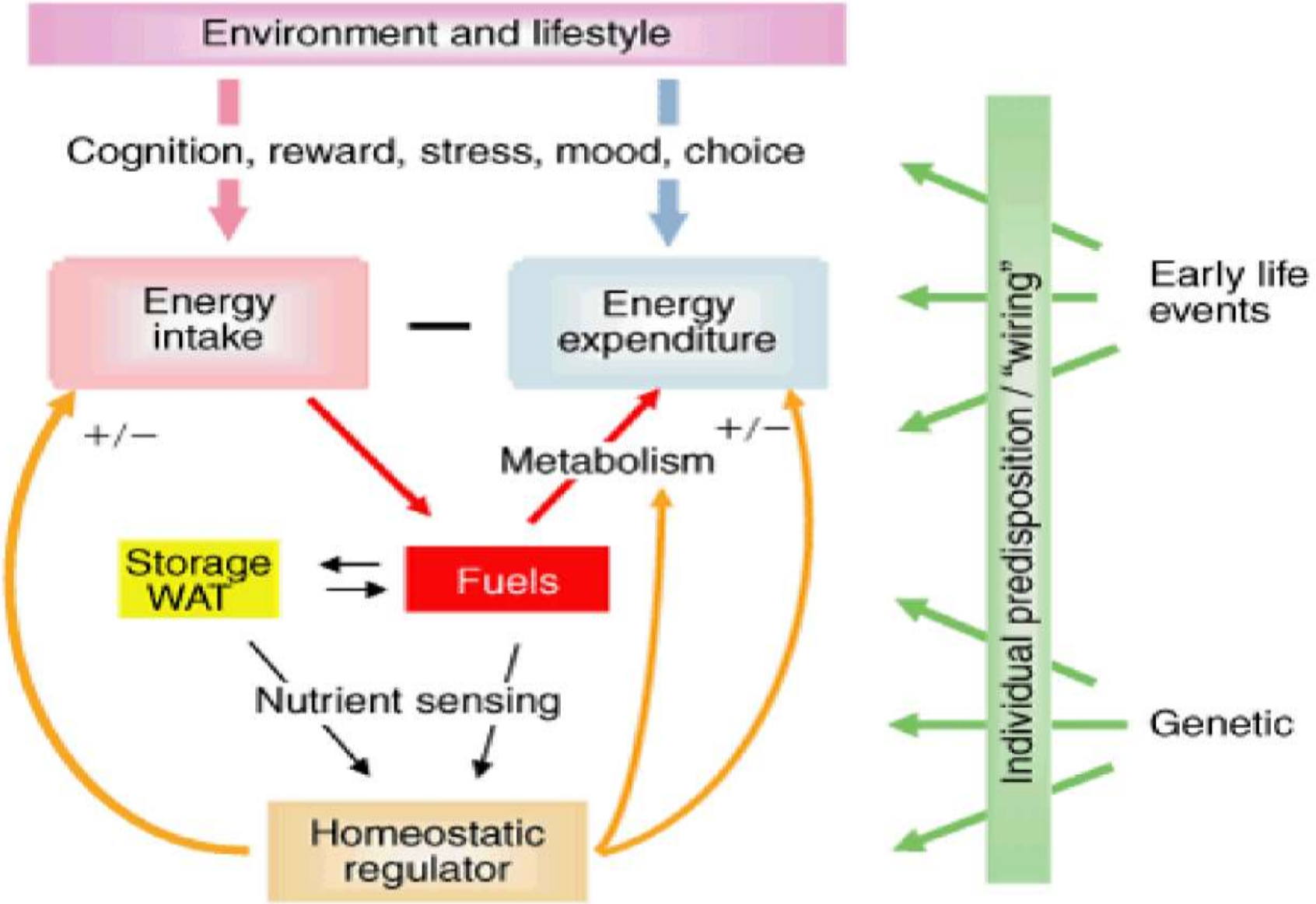
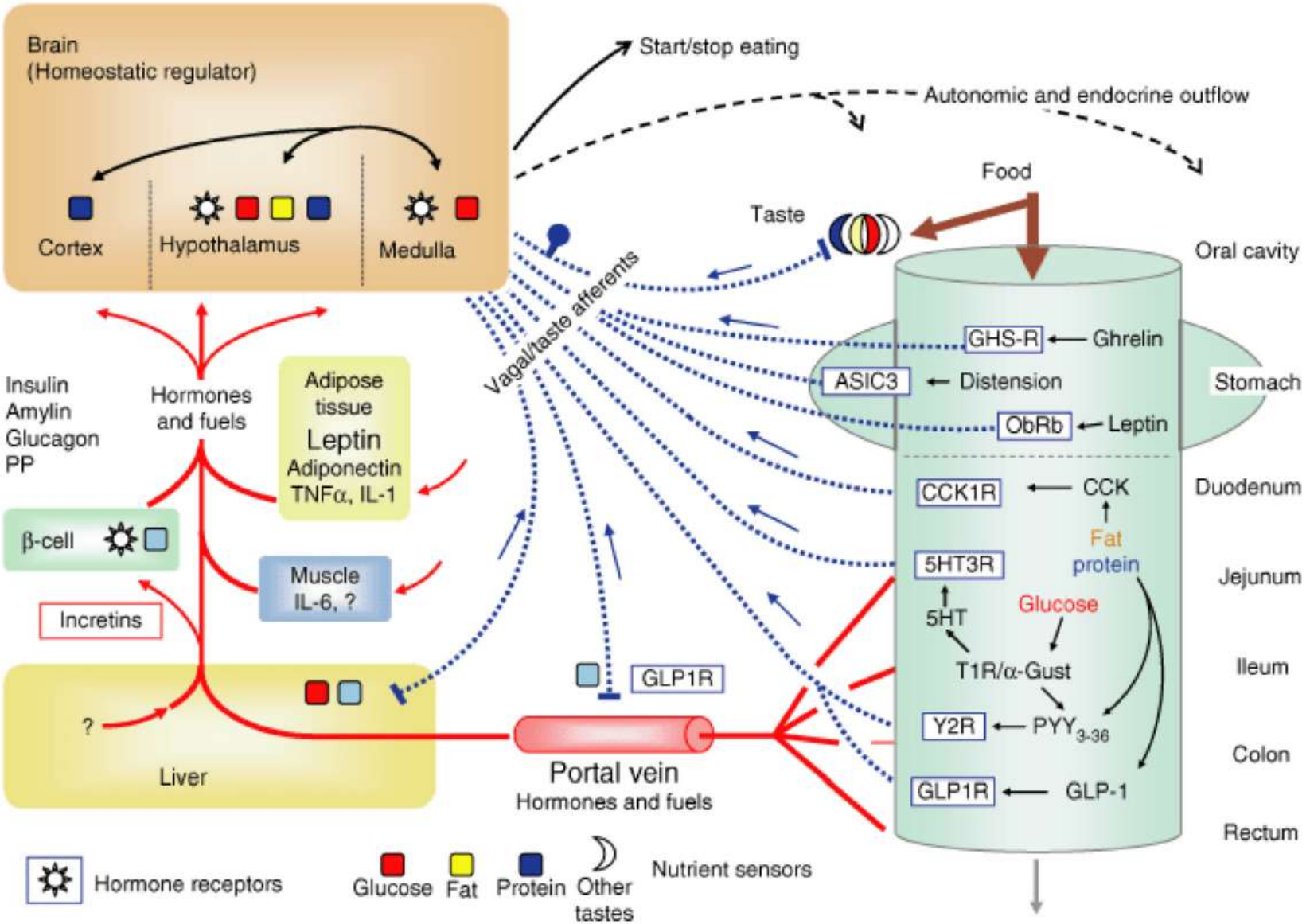


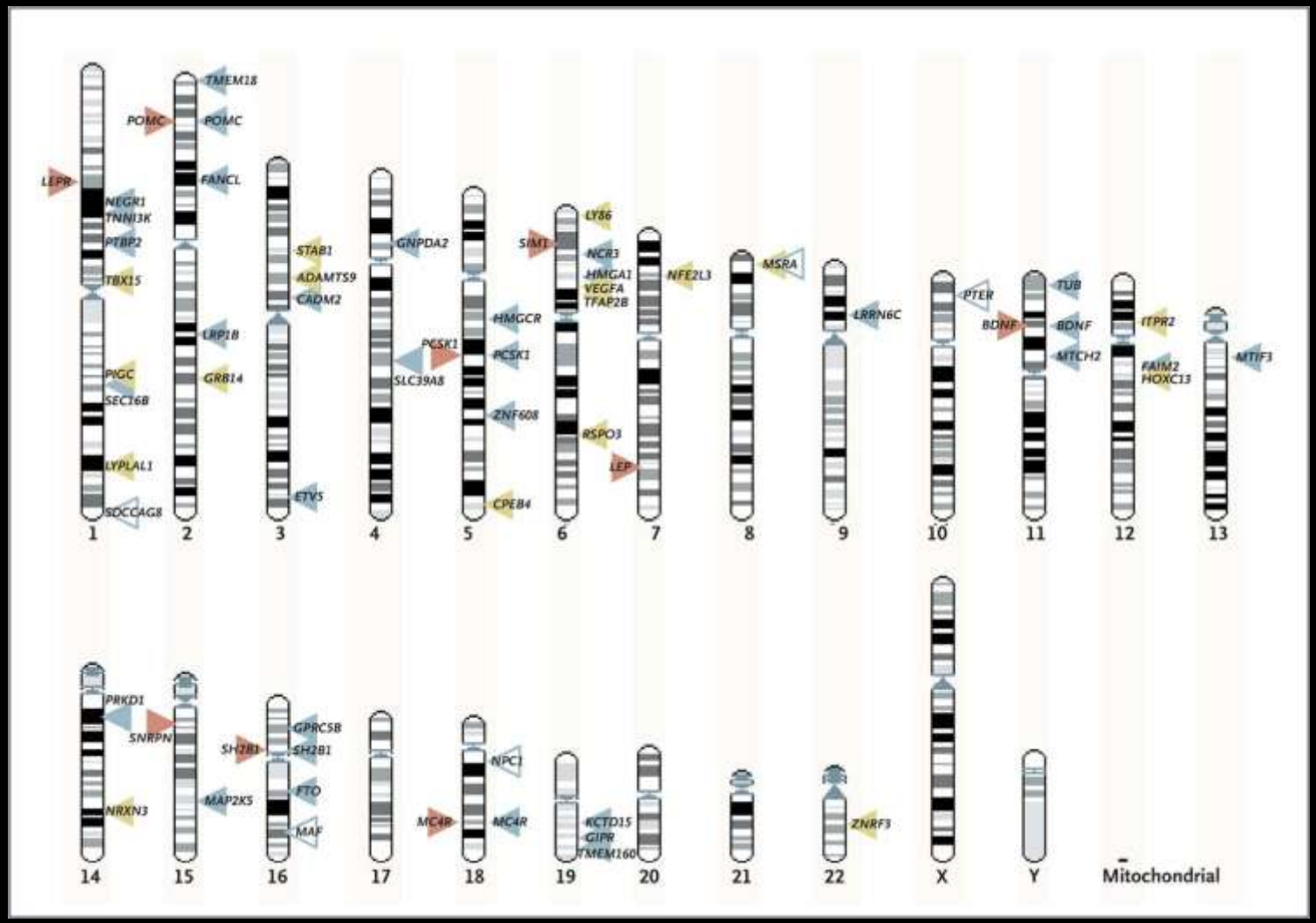
Figure 1.
Major mechanisms and factors determining energy balance.

Obesity (Silver Spring). 2008 December ; 16(Suppl 3): S11–S22.



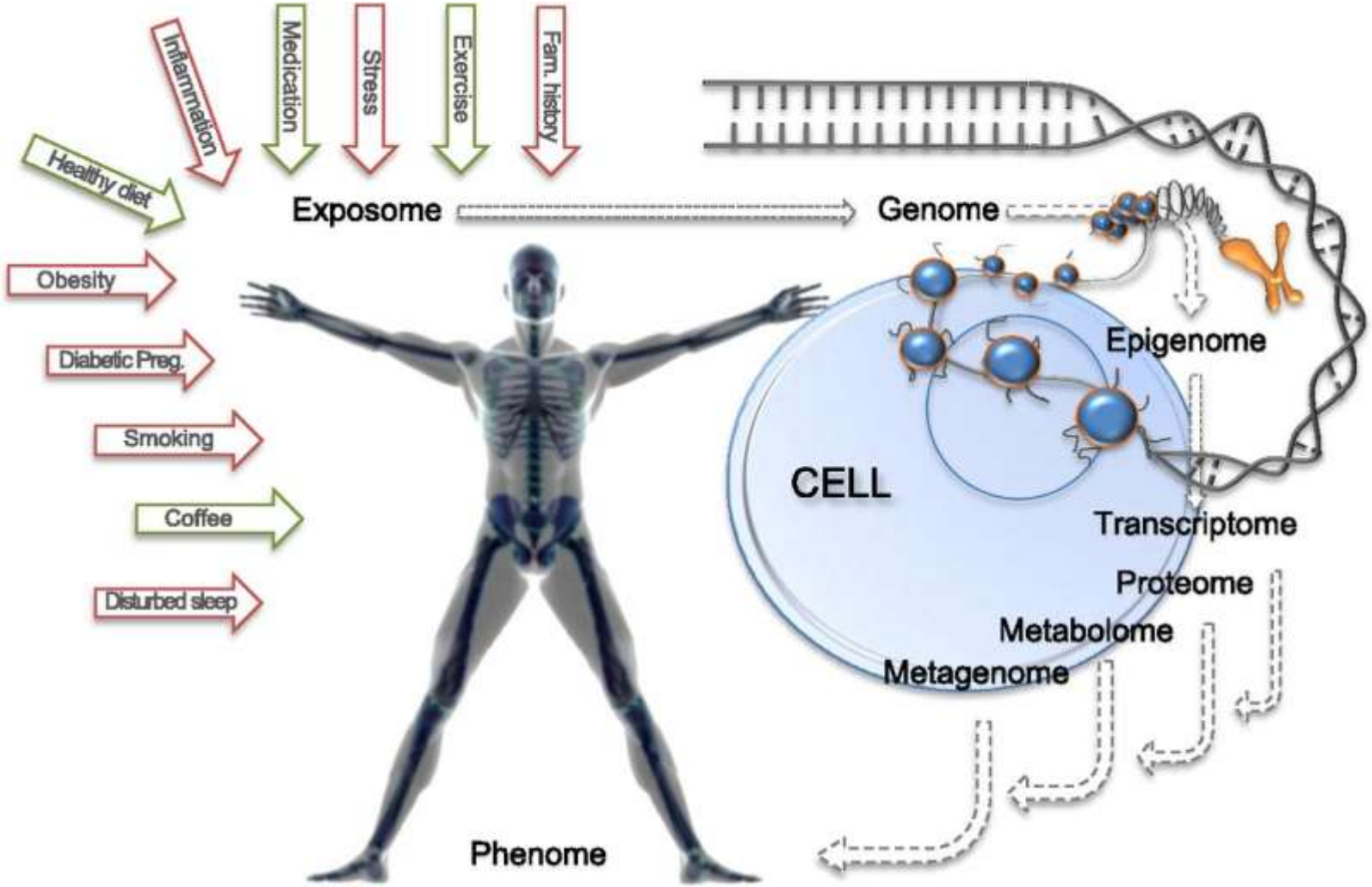
Obesity (Silver Spring). 2008 December ; 16(Suppl 3): S11–S22.

Genomic Locations of Proven Signals of Body-Mass Index (BMI), Obesity, and Related Phenotypes



McCarthy MI. N Engl J Med 2010;363:2339-2350

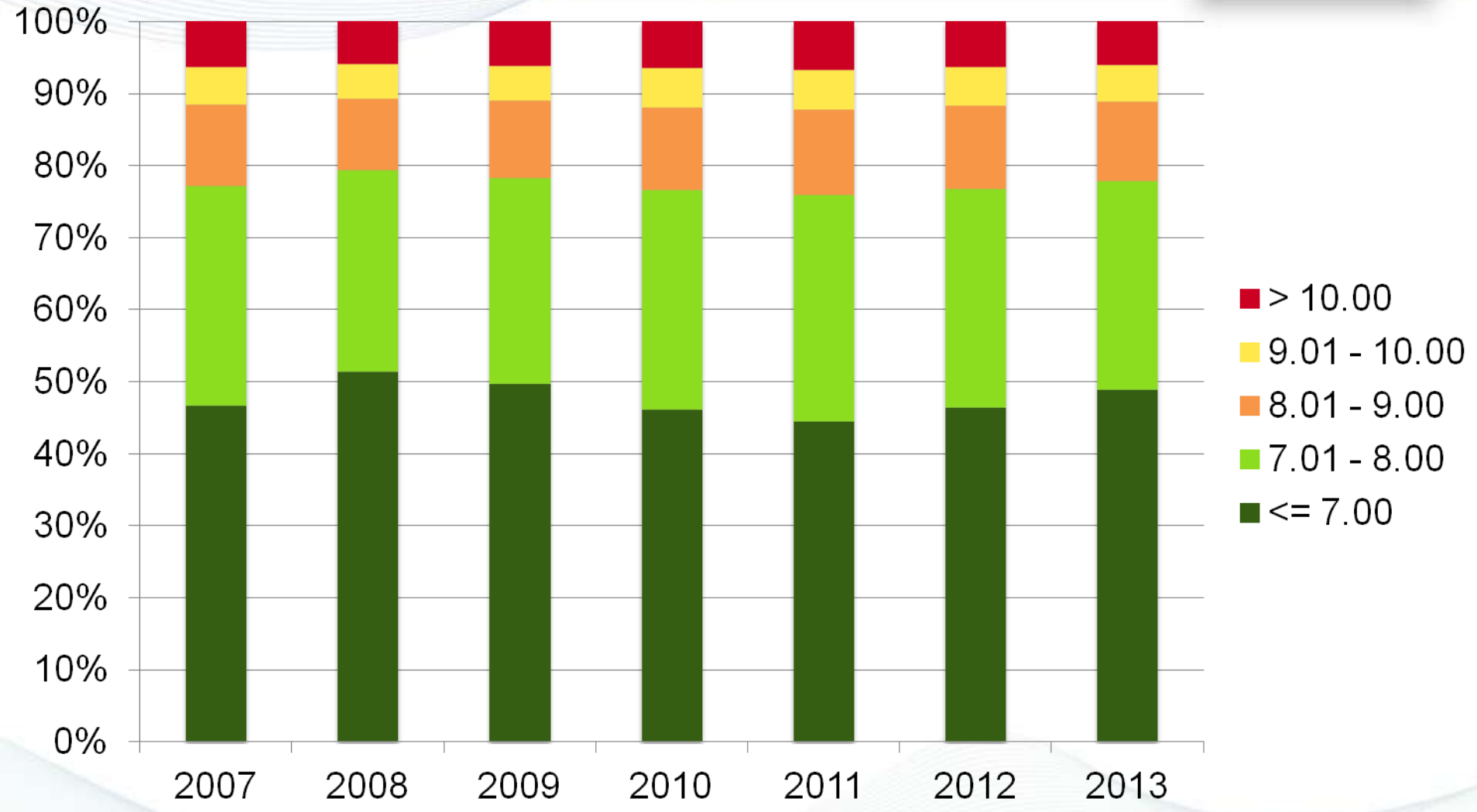
The future of research on stratified diabetes medicine: a systems epidemiology approach to the discovery of interactions between the exposome (all nongenetic elements to which we are exposed) and the quantifiable elements of the human physiome.



Paul W. Franks et al. Dia Care 2013;36:1413-1421

American Diabetes Association.

No. of Diabetes Base Patients with HbA1c Measured



Source: NHG CDMR 2007 – 2013
(Exclusion criteria IMH)

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The crisis in diabetes care in England

Failings identified by recent reports must be tackled urgently

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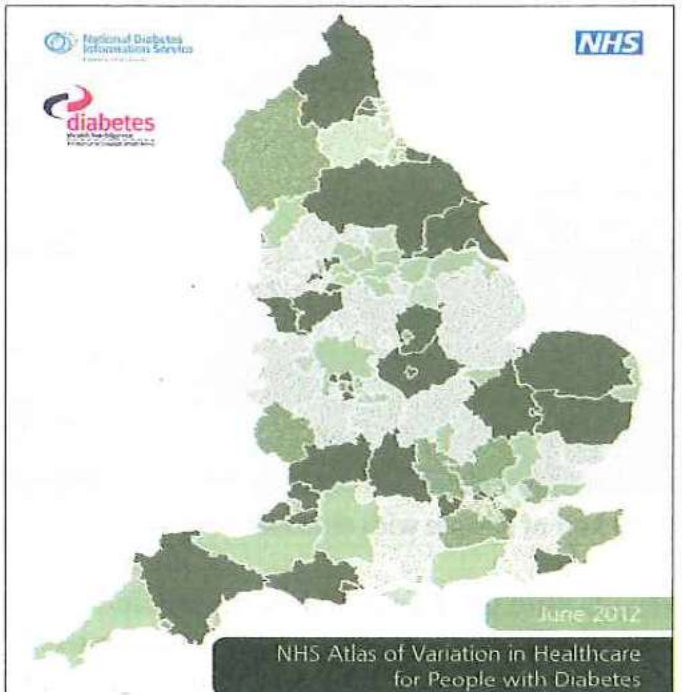
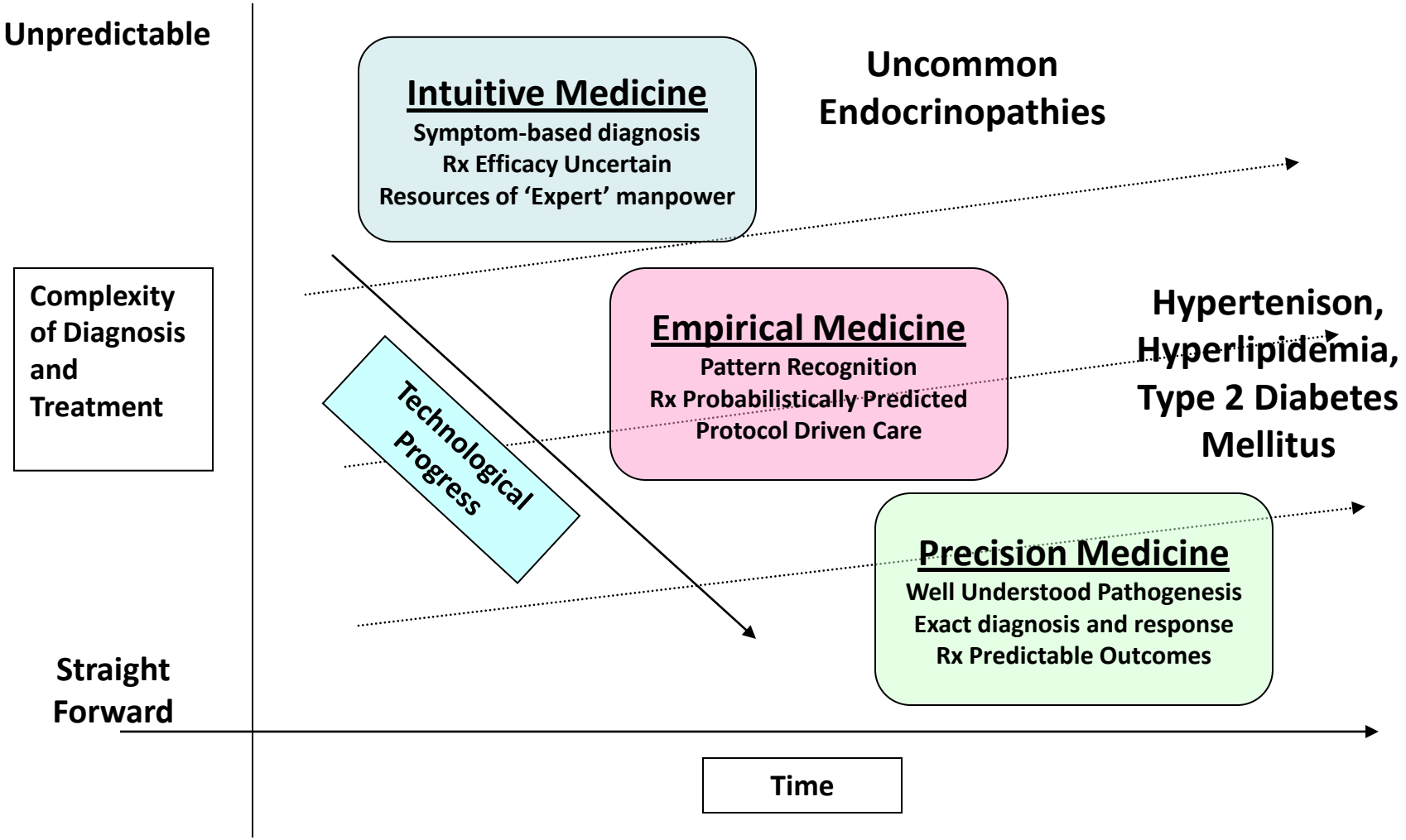
In 2001 the National Service Framework for Diabetes set standards for diabetes care in England, with a delivery strategy designed to achieve a world class diabetes service by 2013.[1] However, a series of recent reports from various sources show just how far we are from delivering the standards by the 2013 deadline. A "state of the nation" report from Diabetes UK declares that diabetes care is "in a state of crisis," and a damning National Audit Office (NAO) report accuses the Department of Health of failing to hold NHS com-

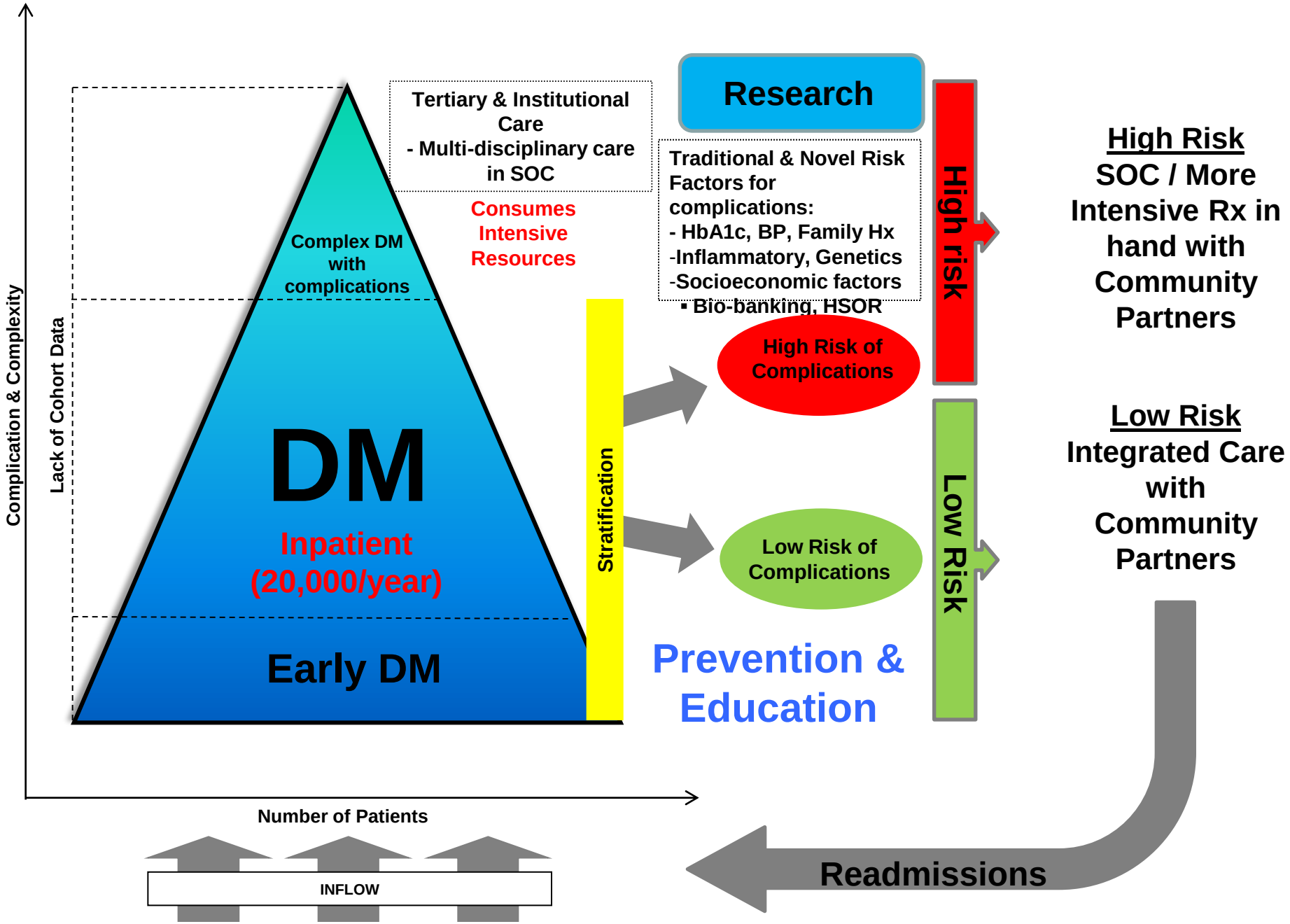


Diabetes – Personalised Medicine



Innovators Prescription - Clayton M Christensen

HSDP Model of Diabetes Care



Trends in Death Rates Among U.S. Adults With and Without Diabetes Between 1997 and 2006

Findings from the National Health Interview Survey

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OBJECTIVE—To determine whether all-cause and cardiovascular disease (CVD) death rates declined between 1997 and 2006, a period of continued advances in treatment approaches and risk factor control, among U.S. adults with and without diabetes.

RESEARCH DESIGN AND METHODS—We compared 3-year death rates of four consecutive nationally representative samples (1997–1998, 1999–2000, 2001–2002, and 2003–2004) of U.S. adults aged 18 years and older using data from the National Health Interview Surveys linked to National Death Index.

RESULTS—Among diabetic adults, the CVD death rate declined by 40% (95% CI 23–54) and all-cause mortality declined by 23% (10–35) between the earliest and latest samples. There was no difference in the rates of decline in mortality between diabetic men and women. The excess CVD mortality rate associated with diabetes (i.e., compared with nondiabetic adults) decreased by 60% (from 5.8 to 2.3 CVD deaths per 1,000) while the excess all-cause mortality rate declined by 44% (from 10.8 to 6.1 deaths per 1,000).

CONCLUSIONS—Death rates among both U.S. men and women with diabetes declined substantially between 1997 and 2006, reducing the absolute difference between adults with and without diabetes. These encouraging findings, however, suggest that diabetes prevalence is likely to rise in the future if diabetes incidence is not curtailed.

Diabetes Care 35:1252–1257, 2012

the U.S. diabetic population since the 1990s, and the intervening years have been a period of continued advances in treatment approaches and risk factor levels. Newly available mortality follow-up data linked to the National Health Interview Survey (NHIS) provide a unique opportunity to determine whether CVD and all-cause mortality has improved among the U.S. population during recent decades as well as whether the excess mortality associated with diabetes has declined (11,12).

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—The NHIS is an ongoing survey of the health status, health care access, and behaviors of the U.S. civilian noninstitutionalized population conducted by the National Center for Health Statistics (NCHS) (11). The NHIS uses multistage probability sampling to select approximately 41,000 households and 107,000 individuals each year. The annual response rate of NHIS between 1997 and 2004 ranged from 87 to 92%. Here, we used