reliable than the much condemned impact factors for journals.[5-7] Also, related publications will be easier to find once they are coded with a unique researcher identifier, not only from indexed but also from non-indexed journals, further improving the assessment of the societal impact of a researcher. Accountability of scientific writing, including an easy and correct display of group authorship, will be further facilitated, as collaborative groups of authors may by linked through ResearcherID.[8] The named ResearcherID Labs feature has recently been added to provide additional data on each member's collaborators.

The Thompson system is a very good start for researcher identification. To facilitate this process, as many researchers as possible should create researcher identification accounts, use their identifiers in their affiliations on all their scientific output, and regularly update their records. Journals could encourage this activity by requiring identification numbers with submission of papers, as is already the case for clinical trial identifiers.

These developments will make science not only easier but also more transparent in a world of increasing digital flow of evidence. The international medical-science community should support the Thompson initiative, and researcher identification in general, and its ongoing development and improvement.

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Type 2 diabetes: pathogenesis and treatment

In the 3 years since our *Lancet* Seminar on type 2 diabetes mellitus,[1] several important developments have taken place. Further evidence that the disease has a strong hereditary component led to a vigorous search to identify candidate genes (table). This approach uncovered two prevalent polymorphisms (in addition to *PPARγ* and *KCNJ11*). *HNF1B* (*MODY5*) bears a polymorphism associated with type 2 diabetes that is inversely related to risk of prostate cancer, suggesting it is important for cell-cycle regulation.[2] Studies of Wolfram's syndrome, a rare diabetic condition, also led to the discovery of a polymorphism in *WFS1* that is associated with type 2 diabetes.[3]

Genome-wide association studies have begun to be successful. This approach first identified *TCF7L2* (transcription-factor-7-like 2 gene), which encodes a transcription factor active in the Wnt-signalling pathway (a complex network of proteins with roles in embryogenesis and cancer).[4] *TCF7L2* variants had a substantially stronger effect than previously identified variants. Six additional genes (regions) were found in data from about 7000 patients with type 2 diabetes and 12 000 controls (table), of which an *SLC30A8* polymorphism was the first.[5-8] Association of the *FTO* polymorphism with type 2 diabetes depends on its risk of obesity, presumably via a hypothalamic effect.[9] A meta-analysis found six new single-nucleotide polymorphisms associated with diabetes, each with a moderate (9–15%) augmentation in diabetes risk.[10] Although these polymorphisms are highly prevalent (30–80% or more of people), they increase risk of diabetes only modestly. From these initial studies, more than a hundred other polymorphisms might be expected to be associated with type 2 diabetes.

Bioinformatics has been used to select a subset of probable gene candidates, by mining sources including sequence data, biological and functional information, and expression levels of candidate genes.[11] Phenotypic metabolic derangements (insulin resistance in key tissues, altered insulin secretion, lipid abnormalities) and bodyweight can be combined with known genetic defects

Gene	Encoded protein(s)	Function of protein	Odds ratio of diabetes-related allele	Putative mechanism
PPARG	Peroxisome-proliferator-activated receptor γ	Nuclear receptor (transcription factor)	1·25	Adipose-tissue-related insulin resistance
KCNJ11	Potassium-inward rectifier 6·2	Potassium channel, β cell	1·12	β-cell dysfunction
WFS1	Wolframin	Activation of endoplasmic reticulum stress-pathway	1·19	β-cell apoptosis
HNF1B	Transcription factor 2	Transcription factor, β-cell development, growth	1·12	β-cell dysfunction
TCF7L2	Transcription-factor-7-like 2	Wnt-signalling, pancreas	1·4	Insulin, glucagon secretion
SLC30A8	Solute carrier family 30, member 8	Zinc transporter in β cell	1·12	β-cell dysfunction
FTO	Fat mass and obesity associated gene protein	2-oxoglutarate-dependent nucleic acid demethylase (brain, hypothalamus expressed)	1·23	Obesity (via insulin resistance)
HHEX or insulin-degrading enzyme region	Haemopoietically expressed homoeobox or insulin-degrading enzyme	..	1·14	HHEX: pancreas or liver development; IDE: insulin action, insulin-release disturbance?
CDKN2A/2B region	Cyclin-dependent kinase inhibitor 2A/2B	Cell-cycle function	1·2	β-cell dysfunction?
IGF2BP2	Insulin-like growth factor 2 mRNA binding protein 2	Transport IGF2 mRNA (translation)	1·17	β-cell function (growth?)
CDKAL1	CDK5-regulatory-subunit-associated-protein 1-like 1	Regeneration	1·12	β-cell development, regeneration
JAZF1	Juxtaposed with another zinc finger gene 1	Encoding repressor of NR2C2, possibly related to growth	1·10	Growth disturbance (pancreas?)
CDC123/CAMK1D region	Cell-division-cycle 123 homologue, calcium or calmodulin-dependent protein kinase D	Possibly related to cell-cycle regulation	1·11	Cell-cycle disturbance (pancreas?)
TSPAN8	Tetraspanin 8	Cell-surface glycoprotein (expressed in pancreas, liver, and colon carcinomas)	1·09	Unknown
THADA	Thyroid-adenoma-associated gene	Possibly involved in apoptosis	1·15	Unknown (apoptosis pancreatic β cells?)
ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif 9	Involved in cleavage of proteoglycans (muscle, pancreas)	1·09	Unknown
NOTCH2	Notch homologue 2	Transmembrane receptor of embryonic pancreatic ductal cells	1·13	Disturbed β-cell development?

Table: **Candidate genes and genetic polymorphisms associated with type 2 diabetes**

of specific monogenic diseases (maturity-onset diabetes of the young, lipodystrophy) or gene-expression data from key tissues. The recognition that diseases might share some patterns of sequence (longer gene length and broader conservation through evolution) further refines these computational methods. Combining bioinformatics with genome-wide association studies might help to identify other candidate genes.

Although lifestyle changes (eg, diet and exercise) remain the cornerstone of diabetes management, the treatment algorithm for type 2 diabetes from the European Association for the Study of Diabetes and the American Diabetes Association suggests that metformin should be started along with lifestyle recommendations at the time of diagnosis. But oral monotherapy with lifestyle changes will not suffice for most patients, necessitating various oral combinations or addition of insulin, each with pros and cons.[12]

Thiazolidinediones have been thought to have cardiovascular protective properties, with seemingly beneficial effects on vascular function, inflammation, oxidative stress, blood pressure and HDL, although they tend to raise total LDL cholesterol. Thiazolidinediones can prevent restenosis after coronary intervention and reduce carotid intima-media thickness, an indicator of atherosclerotic burden. However, in high-risk patients with type 2 diabetes, pioglitazone did not significantly reduce the primary composite endpoint of mortality and macrovascular events compared with placebo (hazard ratio 0·90, 95% CI 0·80–1·02, p=0·095).[13] But the main secondary endpoint of the composite of all-cause mortality, non-fatal myocardial infarction, and stroke was significantly lower in the pioglitazone group (0·84, 0·72–0·98, p=0·027). The difference in HbA_{1c} concentrations between the pioglitazone and placebo group was only 0·5%, suggesting that pioglitazone's antiatherosclerotic effects are distinct from its anti-hyperglycaemic effects.

Rosiglitazone has come under scrutiny for possibly increasing cardiovascular risk, an issue that continues to be debated. Several meta-analyses of mostly short-duration trials that tested glycaemic lowering

rather than cardiovascular outcomes suggested about a 40% increased risk of a myocardial event, besides the well-recognised risk of congestive heart failure with thiazolidinediones. Definitive information might be forthcoming in the next few years from large ongoing randomised trials. Another concern with thiazolidinediones has been the recognition of increased risk of fractures in postmenopausal women, affecting mainly the distal skeleton. Regulators continue to support the position that the benefits of both pioglitazone and rosiglitazone outweigh risks within the approved indications, but that rosiglitazone should not be used in patients with an acute coronary syndrome because it has not been studied in controlled trials in this group.[14]

Endogenous incretin glucagon-like peptide 1 (GLP1) is a postprandially released gut-derived hormone that stimulates insulin secretion, suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite. Patients with type 2 diabetes have decreased GLP1 secretion but a preserved insulinotropic action for GLP1. Because GLP1 is rapidly degraded by dipeptidyl peptidase 4 (DPP4), degradation-resistant GLP1-receptor agonists (incretin mimetics, such as exenatide, liraglutide), and DPP4 inhibitors (incretin enhancers or gliptins, such as sitagliptin, vildagliptin) have been developed. Subcutaneous exenatide and liraglutide reduce fasting, postprandial glucose concentrations, and HbA_{1c} (1–2%), associated with weight loss (2–5 kg). The most common adverse event associated with GLP1-receptor agonists is mild nausea, which decreases over time. Orally administered DPP4 inhibitors reduce HbA_{1c} by 0·5–1·0% (although better lowering of HbA_{1c} has been reported with initial combination with metformin) with few adverse events and they are weight-neutral.[15]

Because long-acting insulin analogues (glargine and detemir) have lower variability in their glucose-lowering effect than neutral protamine Hagedorn insulin, addition of the long-acting analogues to oral hypoglycaemic agents has been studied. Detemir insulin (once or twice daily) led to substantial reductions in HbA_{1c} (from 8·6 to 7·6%), although twice daily biphasic insulin aspart 30 and thrice daily (prandial) insulin aspart led to lower HbA_{1c} concentrations (7·3 and 7·2%, respectively).[16] Glargine insulin once daily also resulted in substantial reductions in HbA_{1c} (from 8·7 to 7·0%), which was non-inferior to thrice daily insulin lispro (mean HbA_{1c} from 8·7% to 6·8%).[17] As might have been expected, both studies showed that the long-acting analogues resulted in lower rates of hypoglycaemia than with the prandial rapid-acting analogues. Clinical judgment will be necessary to establish whether lowering postprandial blood-glucose concentrations with analogue dosing before a meal is offset by the increased risk of hypoglycaemia with this approach.

In the Steno-2 study, patients with microalbuminuria and type 2 diabetes were given an intensified multifactorial intervention (tight regulation of glucose, angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers, aspirin, and lipid-lowering agents). The risk of vascular complications was reduced by about half compared with a conventionally treated group.[18] In a 5·5 year follow-up, despite similar treatment of both groups and disappearance of differences in risk factors (HbA_{1c}, LDL cholesterol, triglycerides, blood pressure) between the groups, risk reduction in the intensively treated group was sustained. The risk of non-fatal cardiovascular events was still reduced by 59% and, most importantly, risk of death from any cause by 57%.

Although progress has been made to improve understanding of some of the genetic components of the pathogenesis of type 2 diabetes, the full complement of the genetic underpinnings of diabetes remains unknown. Type 2 diabetes needs to be managed by many interventions, especially in high-risk patients (eg, with microalbuminuria). Although the safety of some of the agents is under debate, and new agents are finding their way into management, long-term studies to assess efficacy and safety remain needed to guide clinicians.

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Primary endpoints for randomised trials of cancer therapy

Clifford Hudis and colleagues[1] have published guidelines recommending which events should be included in the definition of a range of endpoints. These guidelines are an important contribution, because even the most well-accepted endpoints (such as disease-free survival) have been defined differently in various trials (table), affecting cross-trial comparisons and meta-analyses.

Here, I focus on another issue: which endpoints should be adopted as primary and which as supplementary? Traditionally, disease-free survival (however defined) and overall survival have been regarded as key end-points, both by academic and regulatory bodies. This convention arose at a time when most patients died from their disease, and it represented a pragmatic approach to obtain reliable and reproducible results. However, both endpoints include all deaths, even those that are unrelated to the cancer being treated, and some definitions of disease-free survival also include the occurrence of any unrelated new cancers. The chief merit of these endpoints is simplicity—ie, cause of death does not need to be established. However, the main drawback is lack of specificity for disease-specific outcome, leading to a concomitant loss of power because of the inclusion of outcomes that are not related to disease.

A good example is breast cancer in which only about 30% of diagnosed women will die from their disease and less than 20% from stage I disease.[8] For breast and other good-prognosis cancers, the gain in simplicity outweighs a substantial loss of power for assessment of treatment efficacy. An alternative is to focus primary attention on time to recurrence and time to distant

Trial	Disease-free survival	Time to recurrence	Time to distant recurrence	Death after recurrence*	Overall survival
ATAC[2]	0·85, 0·76–0·94, 0·003	0·76, 0·67–0·87, 0·0001	0·84, 0·72–0·97, 0·022	0·89, 0·74–1·08, 0·23	0·97, 0·86–1·1, 0·7
BIG[3] 1–98	0·82, 0·71–0·95, 0·007	0·78, 0·65–0·92, 0·004	0·81, 0·67–0·98, 0·03	0·81, 0·64–1·03, 0·08	0·91, 0·75–1·1, 0·35
IES[4]	0·76, 0·66–0·88, 0.0001	0·76, 0·65–0·89, 0·0004	0·83, 0·71–0·89, 0·03	0·91, 0·72–1·15, 0·43	0·85, 0·71–1·02, 0·08
ABCSG8/ARNO[5]	0·59*, 0·42–0·81*, 0·0007*	0·60, 0·44–0·81, 0·0009	0·61, 0·42–0·87, 0·0067	0·76, 0·43–1·35, 0·33	0·75*, 0·49–1·13*, 0·16
MA 17[6]	0·58*, 0·44–0·76*, <0·001	0·58, 0·45–0·76, <0·001	0·60, 0·43–0·84, 0·002	0·73, 0·36–1·45, 0·33	0·82, 0·57–1·19, 0·3
ABCSG6a[7]	0·77*, 0·53–1·13*, 0·17*	0·62, 0·40–0·96, 0·031	0·53, 0·29–0·96, 0·034	0·57, 0·26–1·19, 0·11	0·89, 0·59–1·34, 0·57

Data are hazard ratio, 95% CI, p value. *On basis of odds ratios and calculated from published data.

Table: **Endpoints for adjuvant trials of aromatase inhibitors for breast cancer**