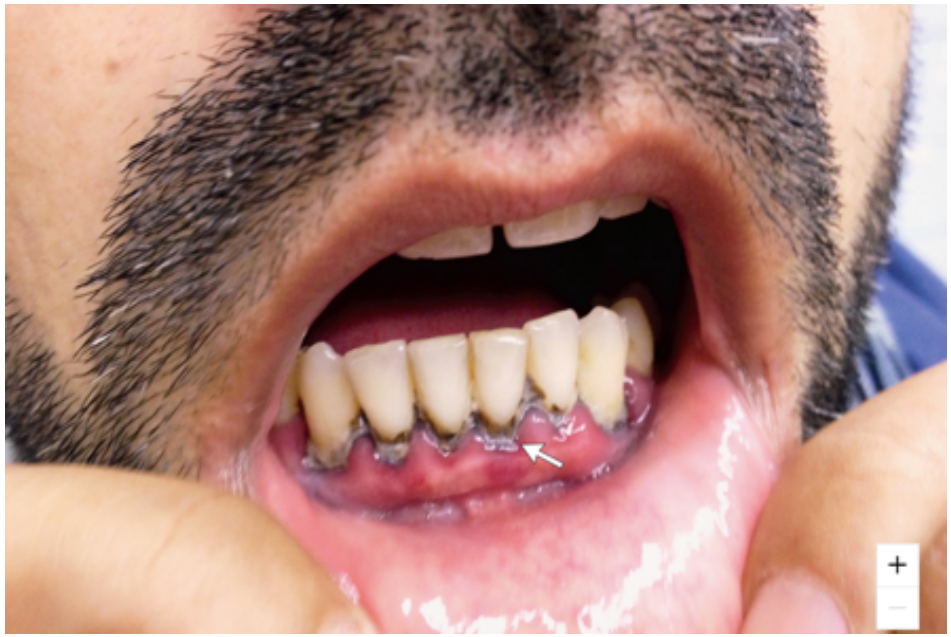
A 39-year-old man presented to the emergency department with a 4-week history of abdominal pain and constipation. Physical examination of the abdomen was normal, but he was noted to have gray lines along the margins of his lower gum. What is the most likely diagnosis?



Scurvy

Bismuth poisoning

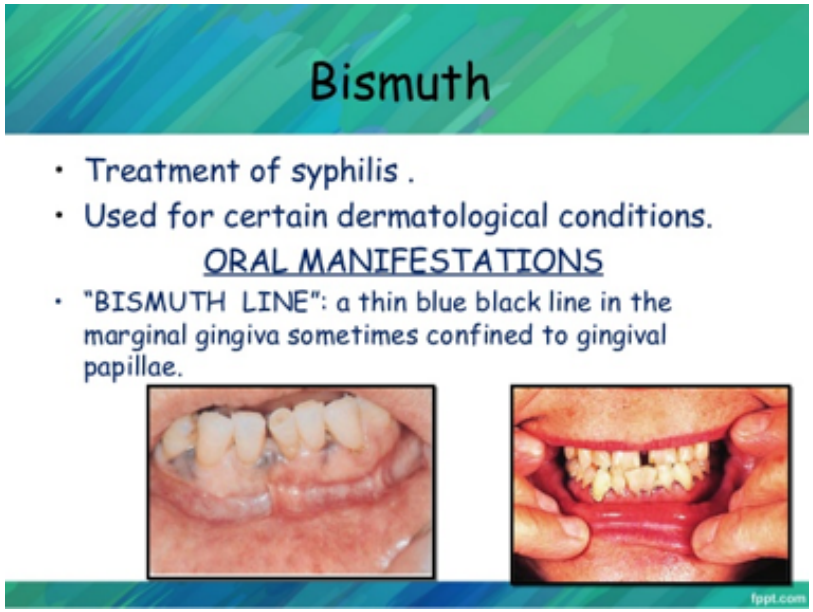
Still ‘s disease

Behcet ‘s Syndrome

Lead poisoning

The correct answer is lead poisoning. The gray lines on the gums are Burton’s line, which is a sign of chronic lead intoxication that develops when lead reacts with oral bacteria metabolites. The patient had a 10-year history of chewing opium. Lead is sometimes added to opium to increase its weight when sold. The patient was treated with chelating agents and counseled to stop chewing opium. At his 7 month follow-up, he had resolution of his symptoms, and Burton’s line had diminished.

Bismut oder Wismut (veraltet auch: Wismuth) ist ein chemisches Element mit dem Elementsymbol Bi und der Ordnungszahl 83. Im Periodensystem steht es in der 5. Hauptgruppe oder Stickstoffgruppe.
Es ist kein stabiles Isotop bekannt. Die durch extrem lange Halbwertszeit äußerst geringe Radioaktivität des natürlich vorkommenden 209Bi ist jedoch für den praktischen Gebrauch ohne Bedeutung. Die Radioaktivität konnte erst 2003 nachgewiesen werden, da vorher die dazu nötigen hochempfindlichen Methoden zur Messung nicht verfügbar waren; noch in den 1990er Jahren galt 209Bi als das schwerste stabile Nuklid.
Bismutverbindungen wie Dibismut-tris(tetraoxodialuminat), Bismutoxidnitrat (Bismutsubnitrat, basisches Bismutnitrat) finden als Bestandteil einer antibiotischen Therapie gegen den Erreger Helicobacter pylori Verwendung, der in Magen und Duodenum Geschwüre verursachen kann (Eradikationstherapie). Die Anwendung erfolgt als sogenannte Quadrupel-Therapie (Kombinationstherapie aus einem Protonenpumpenhemmer und einer Bismut-Triple-Therapie [Bismut Salz, Tetracyclin, Metronidazol]
Eine Bismutvergiftung (Bismutismus) ist aufgrund der schlechten Resorption im Magen-Darm-Trakt selten. Bismuthvergiftung gibt es. Sie ähnelt weitgehend einer Quecksilbervergiftung. Typisch sind das Auftreten eines schiefergrauen bis schwarzen Bismutsaums (Bismutsulfid-Ablagerung) an der Mundschleimhaut mit Ausbildung einer Mundschleimhautentzündung (Stomatitis) und Gingivitis (mit Zahnlockerung, -ausfall), Darmentzündungen (Enteritis) mit Durchfällen sowie Nierenschäden (Bismutnephropathie).



One-Year Outcomes after PCI Strategies in Cardiogenic Shock

Among patients with acute myocardial infarction, cardiogenic shock, and multivessel coronary artery disease, the risk of a composite of death from any cause or severe renal failure leading to renal-replacement therapy at 30 days was found to be lower with percutaneous coronary intervention (PCI) of the culprit lesion only than with immediate multivessel PCI. We evaluated clinical outcomes at 1 year. We randomly assigned 706 patients to either culprit-lesion-only PCI or immediate multivessel PCI. The results for the primary end point of death or renal-replacement therapy at 30 days have been reported previously. Prespecified secondary end points at 1 year included death from any cause, recurrent myocardial infarction, repeat revascularization, rehospitalization for congestive heart failure, the composite of death or recurrent infarction, and the composite of death, recurrent infarction, or rehospitalization for heart failure. Criteria for cardiogenic shock included a systolic blood pressure of less than 90 mm Hg for longer than 30 minutes or the use of catecholamine therapy to maintain a systolic pressure of at least 90 mm Hg, clinical signs of pulmonary congestion, and signs of impaired organ perfusion with at least one of the following manifestations: altered mental status, cold and clammy skin and limbs, oliguria with a urine output of less than 30 ml per hour, or an arterial lactate level of more than 2.0 mmol per liter.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Culprit-Lesion-Only PCI Group (N = 344)	Multivessel PCI Group (N = 342)
Age — yr		
Median	70	70
Interquartile range	60–78	60–77
Male sex — no./total no. (%)	257/343 (74.9)	267/342 (78.1)
Body-mass index†		
Median	26.6	26.7
Interquartile range	24.2–29.4	24.7–29.4
Cardiovascular risk factors — no./total no. (%)		
Current smoking	85/334 (25.4)	89/325 (27.4)
Hypertension	200/339 (59.0)	206/335 (61.5)
Hypercholesterolemia	112/338 (33.1)	116/333 (34.8)
Diabetes mellitus	102/337 (30.3)	116/335 (34.6)
Previous myocardial infarction — no./total no. (%)	60/339 (17.7)	53/335 (15.8)
Previous stroke — no./total no. (%)	29/341 (8.5)	20/336 (6.0)
Known peripheral artery disease — no./total no. (%)	43/341 (12.6)	37/337 (11.0)
Previous PCI — no./total no. (%)	64/339 (18.9)	63/335 (18.8)
Previous coronary-artery bypass grafting — no./total no. (%)	20/341 (5.9)	13/337 (3.9)
Resuscitation before randomization — no./total no. (%)	177/341 (51.9)	189/342 (55.3)
ST-segment elevation myocardial infarction — no./total no. (%)	206/335 (61.5)	209/330 (63.3)
Systolic blood pressure — mm Hg		
Median	100	100
Interquartile range	83–120	85–130
Diastolic blood pressure — mm Hg		
Median	60	61
Interquartile range	50–80	50–80
Mean blood pressure — mm Hg		
Median	76	76
Interquartile range	63–92	63–93
Use of catecholamine — no./total no. (%)	304/344 (88.4)	309/339 (91.2)
Creatinine — mg/dl‡		
Median	1.17	1.20
Interquartile range	0.90–1.66	0.90–1.68
Creatinine clearance — ml/min		
Median	64	66
Interquartile range	42–95	43–93
No. of affected vessels — no./total no. (%)		
1	3/343 (0.9)	2/342 (0.6)
2	122/343 (35.6)	124/342 (36.3)
3	218/343 (63.6)	216/342 (63.2)
Vessel related to the infarction — no./total no. (%)		
Left anterior descending artery	132/343 (38.5)	156/342 (45.6)
Left circumflex artery	76/343 (22.2)	70/342 (20.5)
Right coronary artery	102/343 (29.7)	89/342 (26.0)
Left main artery	31/343 (9.0)	22/342 (6.4)
Bypass graft	2/343 (0.6)	5/342 (1.5)
≥1 Chronic total occlusion — no./total no. (%)	77/344 (22.4)	82/342 (24.0)
Left ventricular ejection fraction — %		
Median	33	30
Interquartile range	25–40	21–40

* There were no significant differences between the two groups in baseline characteristics. PCI denotes percutaneous coronary intervention.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

Immediate crossover occurred in 43 patients (12.5%) in the culprit-lesion-only PCI group and in 32 patients (9.4%) in the multivessel PCI group. Among patients who received stents, drug-eluting stents were used in 93.6% of the patients in the culprit-lesion-only PCI group and in 95.1% in the multivessel PCI group. There was no significant difference between the two groups in the Thrombolysis in Myocardial Infarction grade for epicardial perfusion before or after PCI of the culprit artery. The overall dose of contrast material was significantly greater and the duration of fluoroscopy was significantly longer in the multivessel PCI group than the culprit-lesion-only PCI group.

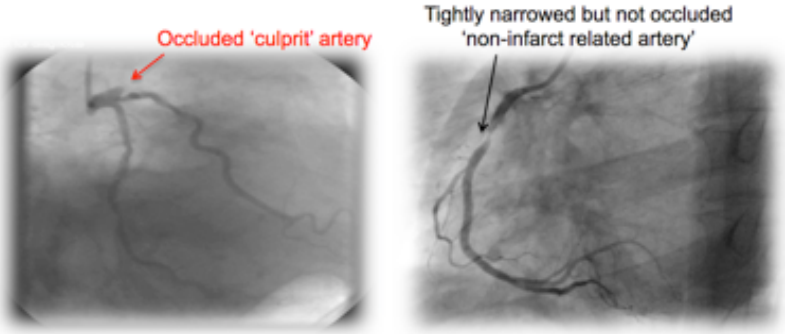


Table 2. Procedural Characteristics.

Variable	Culprit-Lesion-Only PCI Group (N = 344)	Multivessel PCI Group (N = 342)	P Value
Arterial access — no./total no. (%)			
Femoral	287/343 (83.7)	277/342 (81.0)	0.36
Radial	61/343 (17.8)	66/342 (19.3)	0.61
Brachial	2/343 (0.6)	1/342 (0.3)	>0.99
Stent in culprit lesion — no./total no. (%)			
Any	326/343 (95.0)	324/342 (94.7)	0.86
Bare metal	20/326 (6.1)	17/324 (5.2)	0.63
Drug eluting	305/326 (93.6)	308/324 (95.1)	0.41
Bioresorbable scaffold in culprit lesion — no./total no. (%)	2/326 (0.6)	3/324 (0.9)	0.69
TIMI grade for blood flow — no./total no. (%)*			
Before PCI of culprit lesion			0.49
0	189/339 (55.8)	178/337 (52.8)	
I	37/339 (10.9)	45/337 (13.4)	
II	56/339 (16.5)	50/337 (14.8)	
III	57/339 (16.8)	64/337 (19.0)	
After PCI of culprit lesion			0.46
0	13/342 (3.8)	16/338 (4.7)	
I	12/342 (3.5)	8/338 (2.4)	
II	28/342 (8.2)	21/338 (6.2)	
III	289/342 (84.5)	293/338 (86.7)	
Immediate PCI of nonculprit lesions — no./total no. (%)	43/344 (12.5)	310/342 (90.6)	<0.001
Immediate complete revascularization achieved — no./total no. (%)	26/344 (7.6)	277/342 (81.0)	<0.001
Total dose of contrast material — ml			<0.001
Median	190	250	
Interquartile range	140–25	200–350	
Total duration of fluoroscopy — min			<0.001
Median	13	19	
Interquartile range	7–20	12–29	
Staged PCI of nonculprit lesions within 30 days — no./total no. (%)	60/344 (17.4)	8/341 (2.3)	<0.001
Staged coronary-artery bypass grafting within 30 days — no./total no. (%)	1/344 (0.3)	0/341 (0)	>0.99
Mechanical circulatory support — no./total no. (%)	99/344 (28.8)	95/342 (27.8)	0.77
Mechanical ventilation — no./total no. (%)	273/344 (79.4)	282/339 (83.2)	0.20
Subsequent medications in patients who survived until hospital discharge — no./total no. (%)			
Statin	184/195 (94.4)	152/165 (92.1)	0.40
Beta-blocker	181/195 (92.8)	148/165 (89.7)	0.29
Angiotensin-converting–enzyme inhibitor or angiotensin II type 1 receptor antagonist	176/195 (90.3)	140/165 (84.8)	0.12
Aspirin	191/195 (97.9)	163/165 (98.8)	0.54
Clopidogrel	89/195 (45.6)	73/165 (44.2)	0.79
Prasugrel	67/195 (34.4)	56/165 (33.9)	0.93
Ticagrelor	78/195 (40.0)	65/165 (39.4)	0.91

* Thrombolysis in Myocardial Infarction (TIMI) grades for blood flow range from 0 to III, with higher grades indicating better flow. TIMI grades were reported by the investigator.

Table 3. Clinical and Safety Outcomes at 1 Year.*

Outcome	Culprit-Lesion-Only PCI Group (N=344)	Multivessel PCI Group (N=341)	Relative Risk (95% CI)
	no. (%)		
Death from any cause†	172 (50.0)	194 (56.9)	0.88 (0.76–1.01)
Renal-replacement therapy‡	40 (11.6)	56 (16.4)	0.71 (0.49–1.03)
Recurrent myocardial infarction	6 (1.7)	7 (2.1)	0.85 (0.29–2.50)
Death or recurrent infarction	175 (50.9)	199 (58.4)	0.87 (0.76–1.00)
Rehospitalization for congestive heart failure	18 (5.2)	4 (1.2)	4.46 (1.53–13.04)
Death, recurrent infarction, or rehospitalization for heart failure	190 (55.2)	203 (59.5)	0.87 (0.93–1.06)
Repeat revascularization			
Any	111 (32.3)	32 (9.4)	3.44 (2.39–4.95)
PCI	107 (31.1)	29 (8.5)	3.66 (2.50–5.36)
Coronary-artery bypass grafting	4 (1.2)	3 (0.9)	1.32 (0.30–5.86)
Death or renal-replacement therapy	179 (52.0)	203 (59.5)	0.87 (0.76–0.99)
Stroke	15 (4.4)	14 (4.1)	1.06 (0.52–2.17)
Bleeding			
Any	75 (21.8)	86 (25.2)	0.86 (0.66–1.13)
BARC type 2, 3, or 5§	65 (18.9)	79 (23.2)	0.82 (0.61–1.09)

* Confidence intervals were not adjusted for multiple comparisons, and clinical inferences may not be reproducible. Results for clinical end points that were analyzed only for patients who survived are shown in Table S2 in the Supplementary Appendix.

† Causes of death are shown in Table S1 in the Supplementary Appendix.

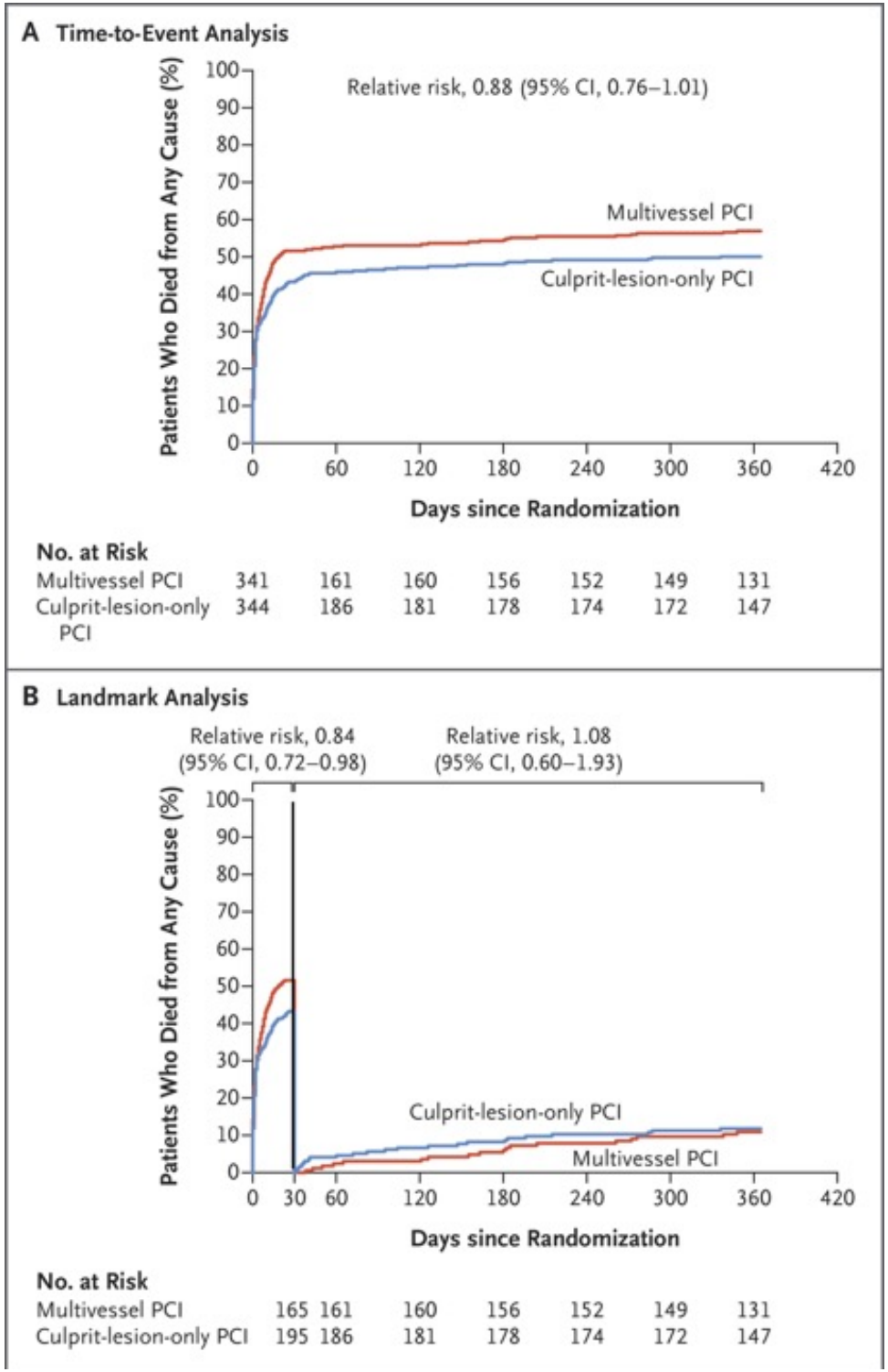
‡ Renal-replacement therapy was defined as any treatment that included dialysis, hemofiltration, or hemodiafiltration.

§ On the Bleeding Academic Research Consortium (BARC) scale, type 2 indicates any overt, actionable sign of bleeding; type 3, bleeding with a decrease in the hemoglobin level of more than 3 g per deciliter, any transfusion, cardiac tamponade, or intracranial or ocular involvement; and type 5, fatal bleeding.

Time-to-Event and Landmark Analyses for Death from Any Cause through 1 Year. Panel A shows Kaplan–Meier estimates of the rate of death from any cause through 1 year. Panel B shows the results of a landmark analysis of the rate of death from any cause through 30 days, as well as the rate between 30 days and 1 year.

Death from cardiovascular causes had occurred in 159 patients (46.2%) in the culprit-lesion-only PCI group and in 180 patients (52.8%) in the multivessel PCI group (relative risk, 0.88; 95% CI, 0.75 to 1.02).

A post hoc landmark analysis revealed a difference between the two groups in mortality within the first 30 days (relative risk, 0.84; 95% CI, 0.72 to 0.98), but mortality was similar in the two groups thereafter (relative risk, 1.08; 95% CI, 0.60 to 1.93). Between 30 days and 1 year, 23 patients (6.7%) died in the culprit-lesion-only PCI group and 18 patients (5.3%) died in the multivessel PCI group. Results for mortality between baseline and 1 year in the intention-to-treat population were similar to results in the per-protocol population (relative risk, 0.87; 95% CI, 0.75 to 1.02) and the as-treated population (relative risk, 0.90; 95% CI, 0.78 to 1.03).



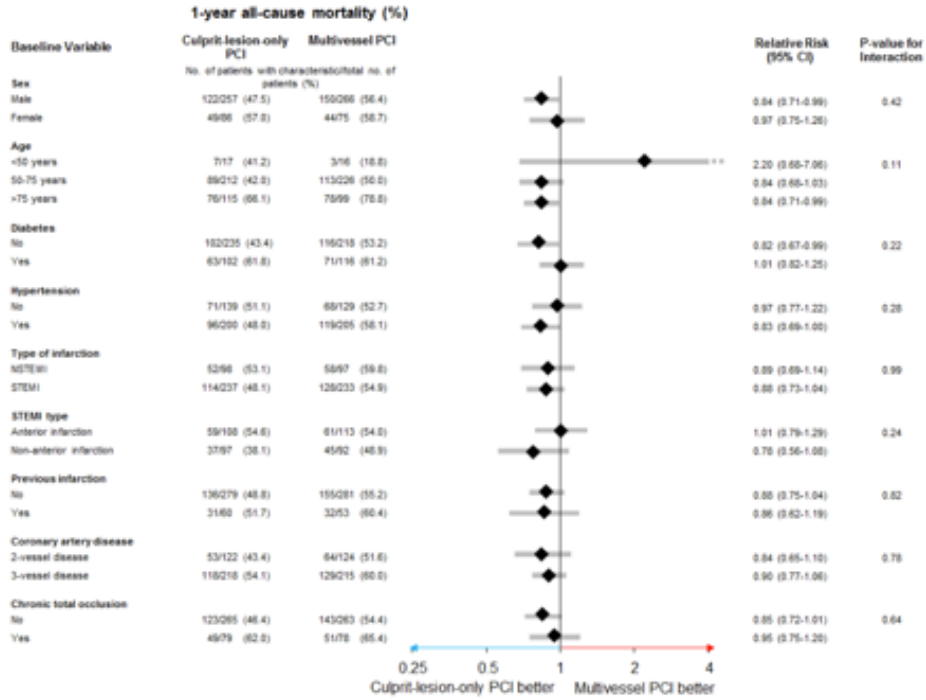
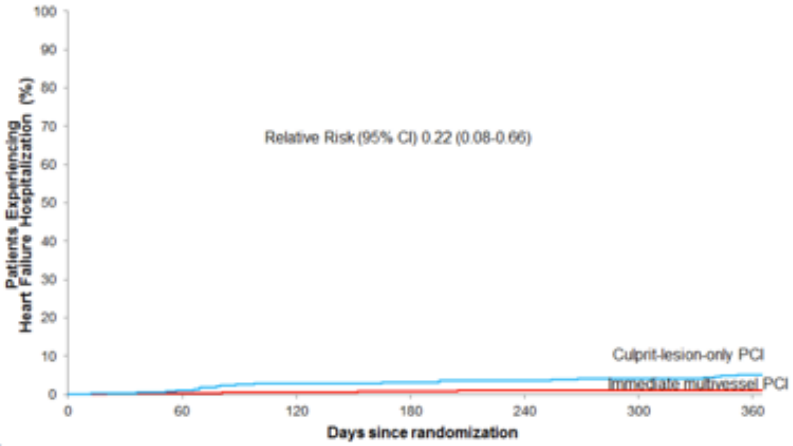


Figure S4 – Time-to-event curves through 1 year for rehospitalization for congestive heart failure

Event rates represent Kaplan-Meier estimates.

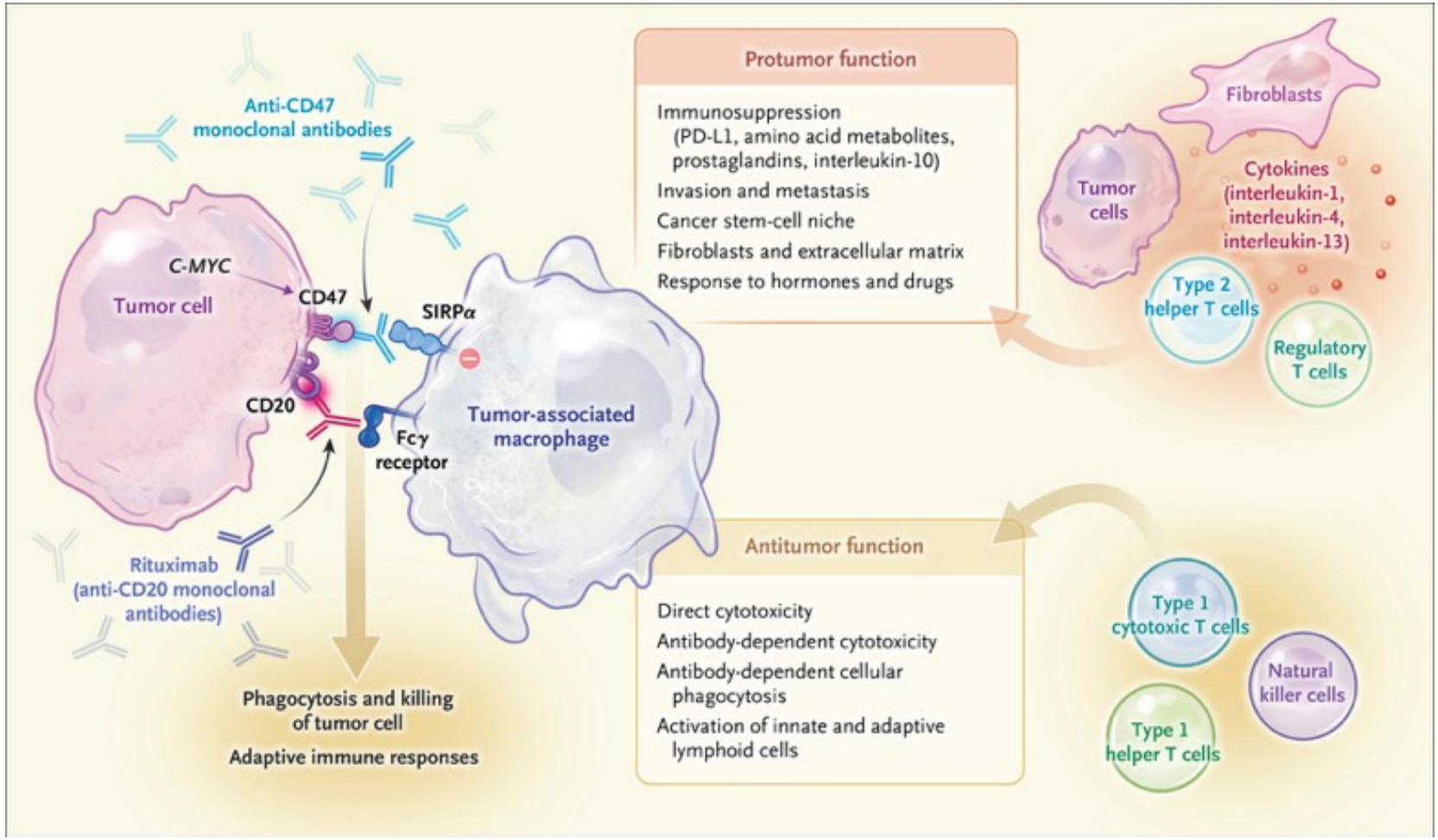
PCI=percutaneous coronary intervention; CI=confidence interval

CHF=congestive heart failure



This multicenter, randomized trial compared culprit-lesion-only PCI (with the option of staged revascularization) with immediate multivessel PCI in patients with acute myocardial infarction, cardiogenic shock, and multivessel coronary artery disease. We previously reported that the risk of a composite of death from any cause or renal-replacement therapy was lower with culprit-lesion-only PCI than with multivessel PCI in the 30-day analysis of this trial. In the analysis reported here, we found that mortality did not differ significantly between the two groups at 1 year. However, the rates of rehospitalization for heart failure and repeat revascularization were higher in the culprit-lesion-only PCI group than the multivessel PCI group at 1 year. This trial has several limitations. First, all the end points in the 1-year analysis are exploratory because the trial was powered for the 30-day analysis of the primary composite end point. Second, blinding was not possible owing to the nature of the intervention performed. In conclusion, this multicenter, randomized trial compared culprit-lesion-only PCI (with the option of staged revascularization) with immediate multivessel PCI in patients with acute myocardial infarction, cardiogenic shock, and multivessel coronary artery disease. At 30 days, the risk of a composite of death from any cause or renal-replacement therapy was significantly lower with culprit-lesion-only PCI than with multivessel PCI. At 1 year, mortality did not differ significantly between the two groups. However, the incidence of rehospitalization for heart failure was higher and repeat revascularization was more frequent with culprit-lesion-only PCI than with multivessel PCI at 1 year.

Macrophage Checkpoint Blockade in Cancer — Back to the Future



Tumor-Associated Macrophages in Cancer Progression and as Therapeutic Targets. Macrophages can exert dual function in patients with cancer, depending on the activation state and therapy. During tumor progression, protumor functions prevail. *C-MYC*, an oncogene that often drives the proliferation of neoplasms, also induces the expression of CD47. Negative signals delivered by the signal regulatory protein α (SIRPα) to macrophages through CD47 prevent their participation in tumor killing. In the presence of antitumor monoclonal antibodies (anti-CD20; rituximab), blocking the CD47–SIRPα checkpoint unleashes macrophage-mediated tumor-cell phagocytosis and killing. The same pathway activates effective adaptive immunity. PD-L1 denotes programmed death ligand 1.

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma

The Hu5F9-G4 (hereafter, 5F9) antibody is a macrophage immune checkpoint inhibitor blocking CD47 that induces tumor-cell phagocytosis. 5F9 synergizes with rituximab to eliminate B-cell non-Hodgkin's lymphoma cells by enhancing macrophage-mediated antibody-dependent cellular phagocytosis. This combination was evaluated clinically. We conducted a phase 1b study involving patients with relapsed or refractory non-Hodgkin's lymphoma. Patients may have had diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma. 5F9 (at a priming dose of 1 mg per kilogram of body weight, administered intravenously, with weekly maintenance doses of 10 to 30 mg per kilogram) was given with rituximab to determine safety and efficacy and to suggest a phase 2 dose.

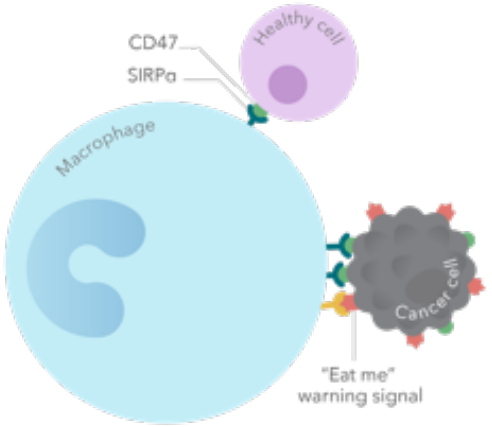
Eligible patients had CD20-expressing B-cell lymphoma that had relapsed or that was refractory to at least two previous lines of therapy.

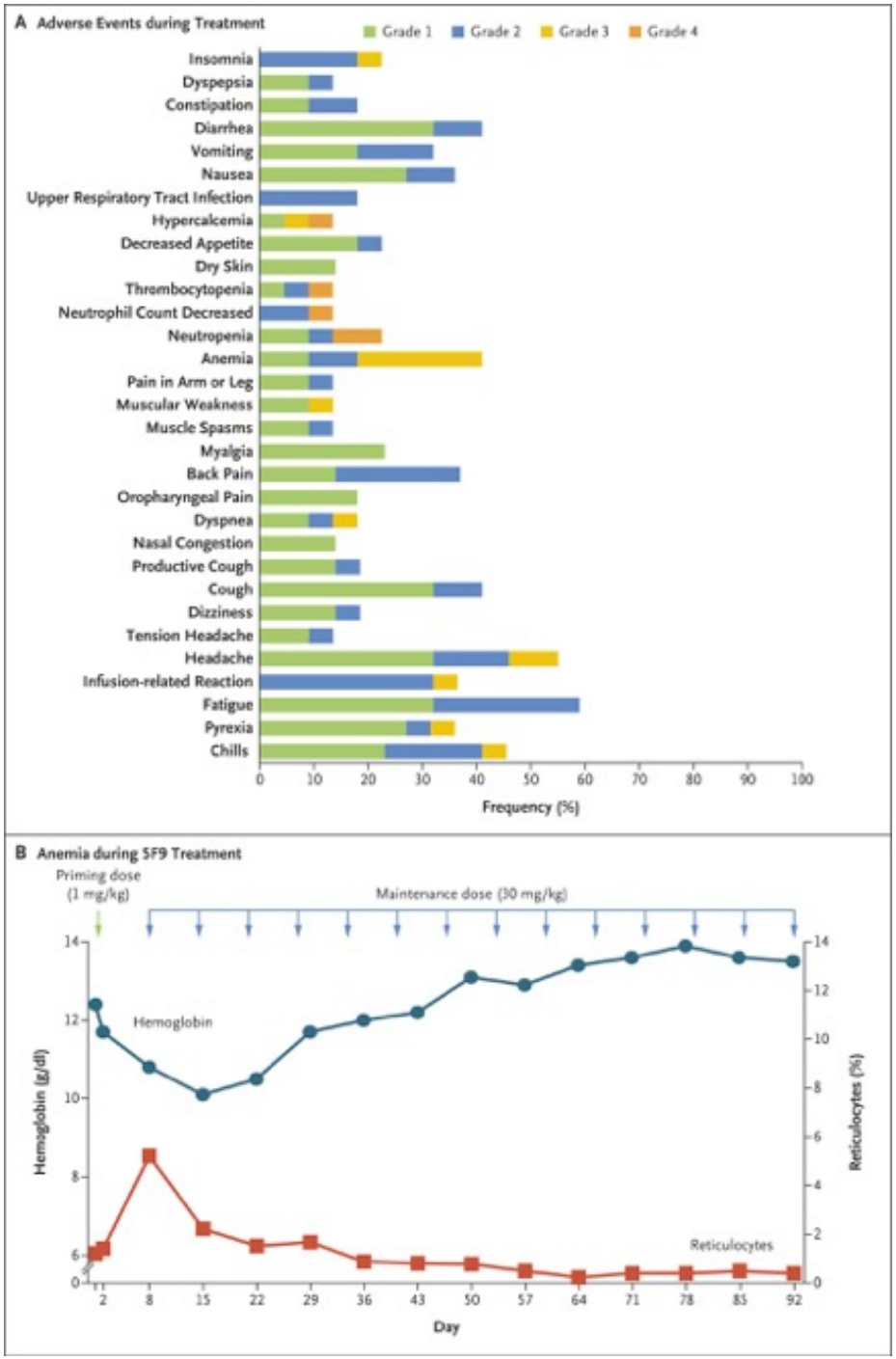
In all the cohorts, rituximab was administered intravenously at a dose of 375 mg per square meter of body-surface area, weekly in cycle 1 starting in week 2, and then monthly in cycles 2 through 6. 5F9 was administered until disease progression occurred, a lack of clinical benefit was determined, or an unacceptable level of toxic effects occurred.

Table 1. Characteristics of the 22 Patients Who Were Treated.*

Characteristic	All Patients (N = 22)	Patients with DLBCL (N = 15)	Patients with Follicular Lymphoma (N = 7)
Median age (range) — yr	59 (44–82)	60 (44–82)	59 (44–75)
Sex — no. (%)			
Male	12 (55)	7 (47)	5 (71)
Female	10 (45)	8 (53)	2 (29)
Median no. of previous therapies (range)	4 (2–10)	4 (2–10)	4 (2–9)
ECOG performance-status score — no. (%)†			
0	7 (32)	3 (20)	4 (57)
1	14 (64)	11 (73)	3 (43)
2	1 (5)	1 (7)	0
Lugano stage at diagnosis — no. (%)‡			
I or II	4 (18)	3 (20)	1 (14)
III or IV	15 (68)	11 (73)	4 (57)
Unknown	3 (14)	1 (7)	2 (29)
Disease refractory to previous rituximab regimen — no. (%)	21 (95)	14 (93)	7 (100)
Disease refractory to most recent regimen — no. (%)	14 (64)	9 (60)	5 (71)
Previous autologous stem-cell transplantation — no. (%)	4 (18)	2 (13)	2 (29)
5F9 maintenance dose level — no. (%)			
10 mg/kg	3 (14)	2 (13)	1 (14)
20 mg/kg	6 (27)	6 (40)	0
30 mg/kg	13 (59)	7 (47)	6 (86)

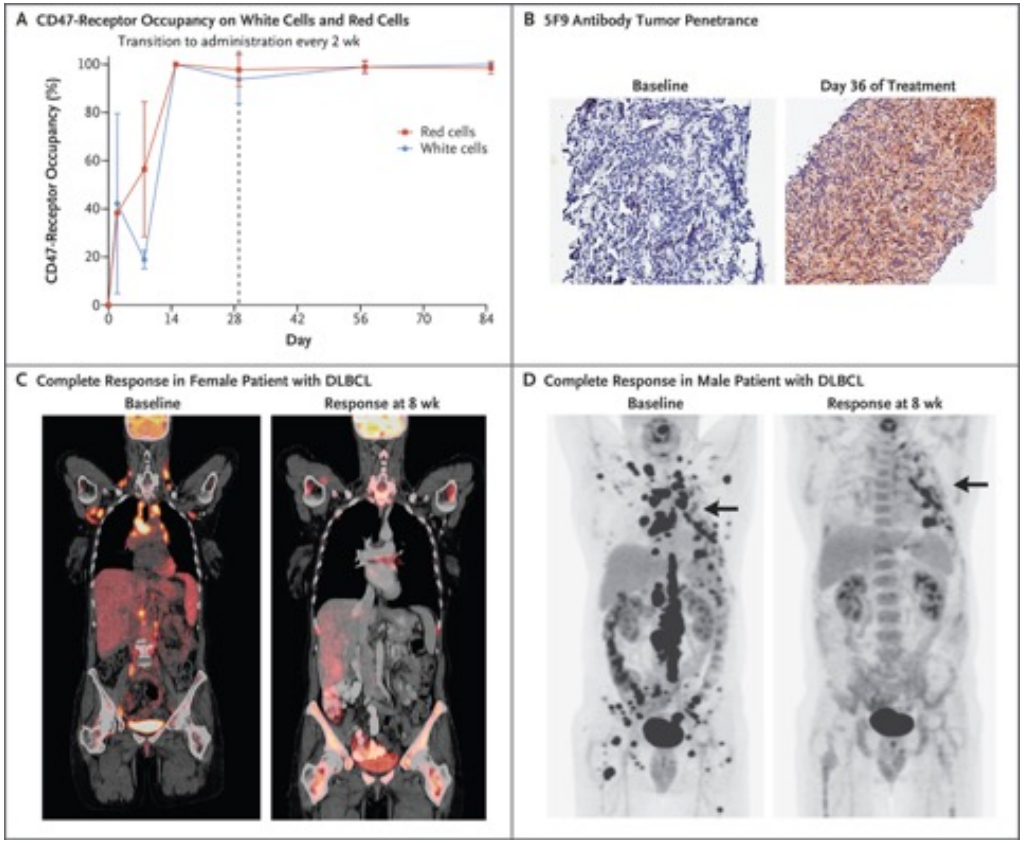
* A total of 15 patients (68%) in this study of Hu5F9-G4 (5F9) had received a diagnosis of diffuse large B-cell lymphoma (DLBCL) and 7 (32%) had received a diagnosis of follicular lymphoma.
† Scores for the Eastern Cooperative Oncology Group (ECOG) performance status are assessed on a 5-point scale, with higher numbers indicating greater disability.
‡ A Lugano stage of I indicates disease involving one lymph node or a group of adjacent nodes, II two or more nodal groups on the same side of the diaphragm, III nodes on both sides of the diaphragm or nodes above the diaphragm with spleen involvement, and IV additional noncontiguous extralymphatic involvement.[18]





Adverse Events Due to Hu5F9-G4 (5F9), Rituximab, or Both and On-Target Anemia Effect of 5F9. Panel A shows the adverse events that occurred in at least 10% of the patients during treatment. Panel B shows the levels of hemoglobin and reticulocytes over time in a representative patient (with diffuse large B-cell lymphoma) during the study. The priming dose of 1 mg of 5F9 per kilogram of body weight was received on day 1 (green arrow). The patient received maintenance doses of 30 mg of 5F9 per kilogram (blue arrows).

Three dose-limiting toxic effects were observed. In cohort 2, a grade 3 pulmonary embolism was seen. This patient had respiratory symptoms during a 5F9 infusion and was later found to have an occult deep venous thrombosis as a result of vascular compression from lymphoma that was probably the source of the pulmonary embolism. The patient had resolution of the symptoms after receipt of anticoagulation and continued receiving treatment until disease progression several weeks later. This toxic effect led to a cohort expansion to six patients, and no additional dose-limiting toxic effects were observed.



Pharmacodynamic Data on CD47-Receptor Occupancy, Tumor Penetrance, and Responses in Two Patients. Panel A shows CD47-receptor occupancy on peripheral white cells and red cells. The dashed vertical line at day 29 shows the transition from receipt of the dose weekly to receipt every 2 weeks. Panel B shows 5F9 antibody tumor penetrance in a tumor supraclavicular lymph node in a patient with DLBCL who was treated with 20 mg of 5F9 per kilogram. 5F9 penetrance was measured by immunohistochemical testing with detection by anti-IgG4 staining. Panel C shows positron-emission tomographic–computed tomographic (CT) scans of a 58-year-old woman (Patient 18) with heavily pretreated DLBCL (four previous lines of therapy) who had had rapid disease progression 3 months after undergoing autologous transplantation. The patient had daily fevers before enrollment, which resolved within a few weeks after the initiation of study therapy. The patient had a complete response at 8 weeks, including resolution of bone marrow disease as assessed by means of bone marrow aspirate and biopsy. Panel D shows CT scans of a 56-year-old man (Patient 16) who had primary refractory DLBCL (two previous lines of therapy) with bulky disease. The patient had a complete remission during treatment. Arrows indicate hypermetabolic pleural thickening from previous surgery and not lymphoma.

Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

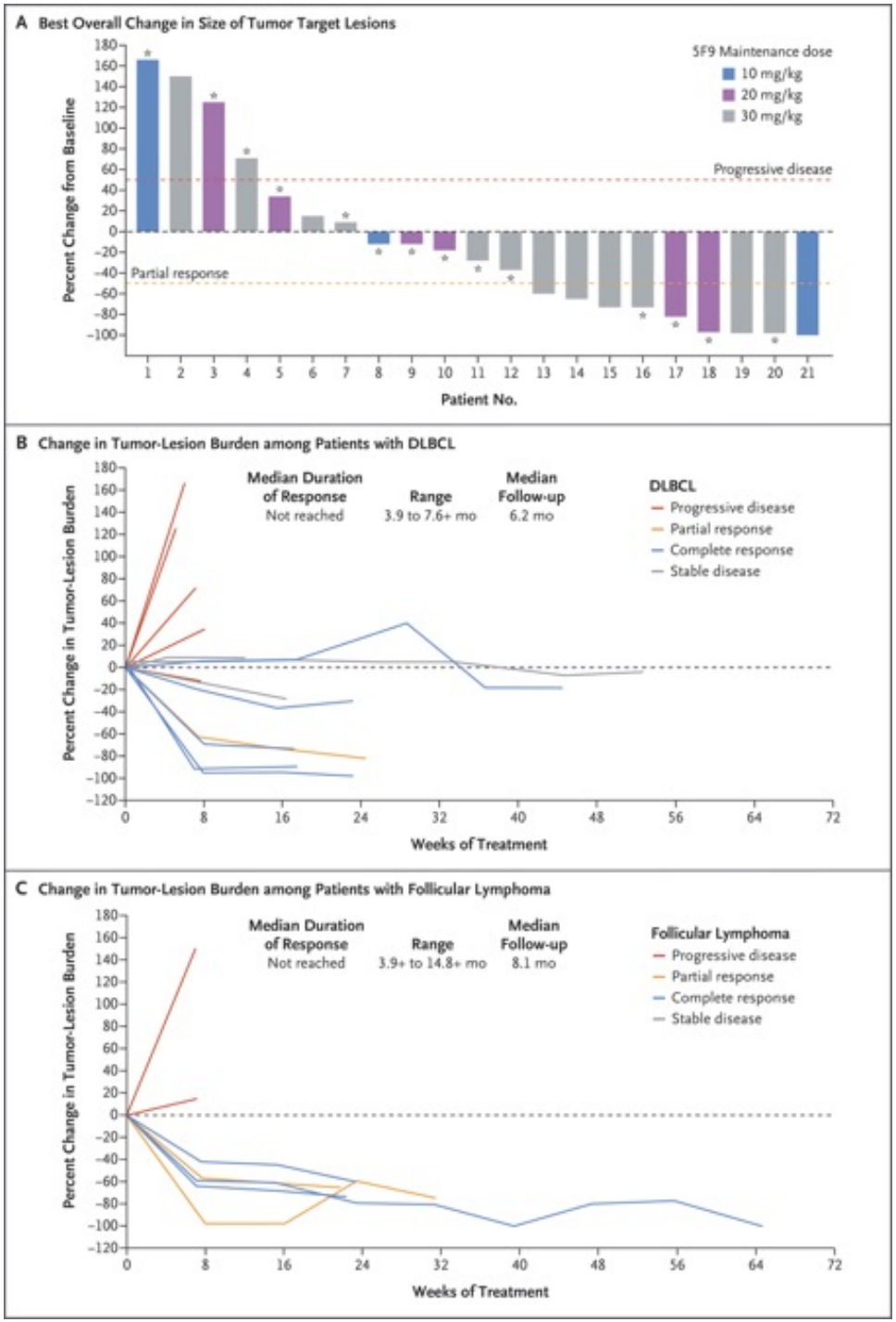
Response	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Objective response	11 (50)	6 (40)	5 (71)
Complete response	8 (36)	5 (33)	3 (43)
Partial response	3 (14)	1 (7)	2 (29)
Stable disease	3 (14)	3 (20)	0
Progressive disease	8 (36)	6 (40)	2 (29)
Disease control	14 (64)	9 (60)	5 (71)

* Objective response was defined as a complete or partial response. Disease control was defined as a complete response, partial response, or stable disease.

In an intention-to-treat analysis, the objective response rate among all the patients was 50%, with 36% of the patients having a complete response. Among patients with DLBCL, the response rate was 40% (6 of 15 patients), with 5 patients (33%) having a complete response. Among patients with follicular lymphoma, the response rate was 71% (5 of 7 patients), with 3 patients (43%) having complete response.

Why CD47 Matters

Cancer cells commandeer a “don’t eat me” signal, called CD47, to escape elimination by our innate immune system’s first responders.These innate immune cells, called macrophages, respond to “eat me” signals, non-specific signs of danger, from pathogens or abnormal cells, including cancer cells. When a macrophage recognizes a cancer cell through its “eat me” signals, it swallows and digests the cancer cell as a first line of defense. The macrophage then alerts specialized cells in the adaptive branch of our immune system, which include T cells, to specific foreign features, antigens, of that cancer cell. This mobilizes targeted, long-term defenses against the cancer cells.



Change in Tumor-Lesion Size and Duration of Responses with 5F9 and Rituximab. Panel A shows a waterfall plot of the best overall change in the size of tumor target lesions among patients with diffuse large B-cell lymphoma (DLBCL; indicated by an asterisk) or follicular lymphoma, according to the maintenance dose received. Plots of the percentage changes in the tumor burden of target lesions are shown graphically. All the tumor lesions were measured in centimeters. A target lesion size of "too small to measure" was imputed as 0.5 cm^2, and "not visible" as 0 cm^2. One patient could not be evaluated because of discontinuation of the study before the first protocol-specified response assessment. Thresholds regarding progressive disease and partial response according to the Lugano criteria[18] are indicated by dashed lines. Per the Lugano criteria, patients met the criteria for response by either a decrease in the tumor lesion size as assessed by computed tomography (data shown) or a decrease in metabolic activity as assessed by positron-emission tomography (data not shown). Panel B shows spider plots of data from patients with DLBCL, according to response to treatment, and Panel C shows data from patients with follicular lymphoma; the median duration of response and median follow-up are also shown. A plus sign indicates that the response was ongoing at the time of data cutoff. The dashed line at 0 indicates no change from baseline.

In this phase 1b study, combination therapy with 5F9 plus rituximab was associated with mainly low-grade toxic effects and produced responses in half the patients with relapsed or refractory aggressive and indolent lymphomas. Chemoimmunotherapy is the standard approach for the treatment of B-cell lymphoma but may not be appropriate in patients with relapsed or refractory disease or in patients who cannot receive chemotherapy. Recent biologic insights regarding immune evasion by lymphomas have enabled the development of multiple promising immunotherapeutic strategies. 5F9 is an anti-CD47 antibody that inhibits a key macrophage checkpoint and facilitates macrophage destruction of lymphoma cells. When the drug is administered with a tumor-targeting antibody such as rituximab, a synergistic enhancement of “eat me” signals promotes disease elimination. The safety profile of 5F9 plus rituximab showed no unacceptable side effects, and the maximum tolerated dose was not reached.

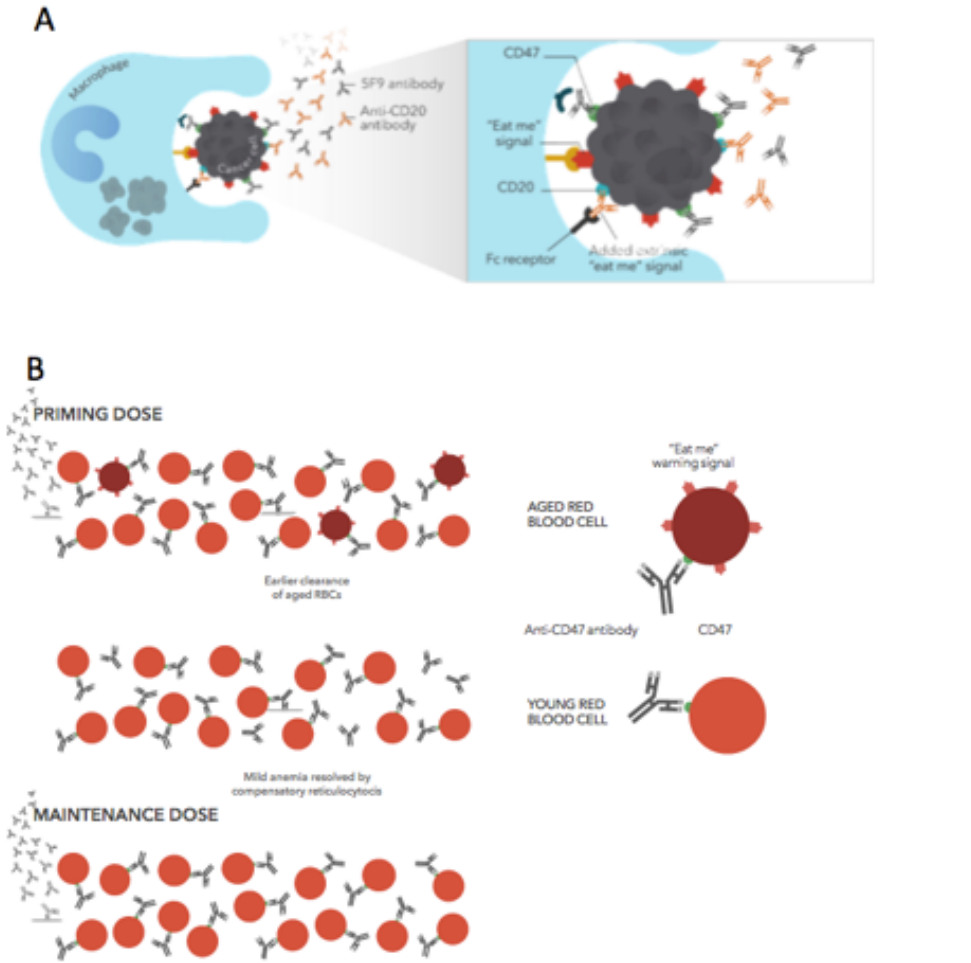
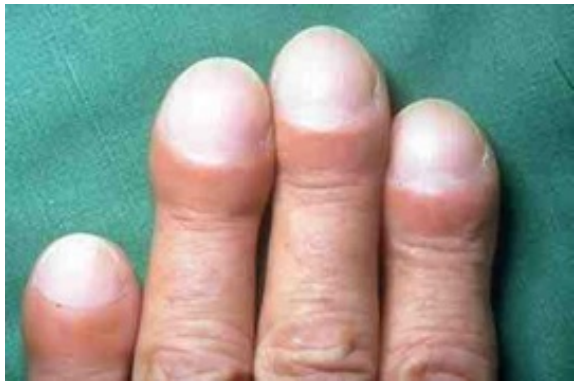
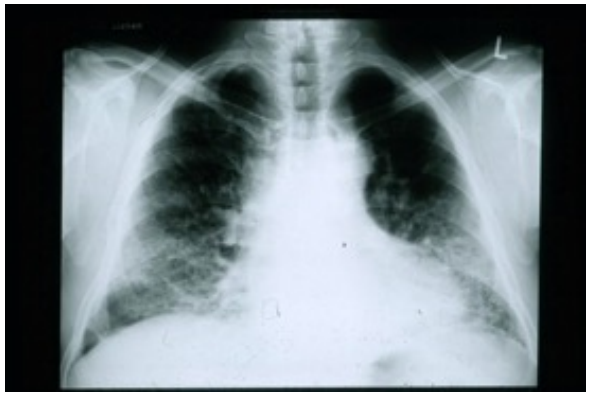
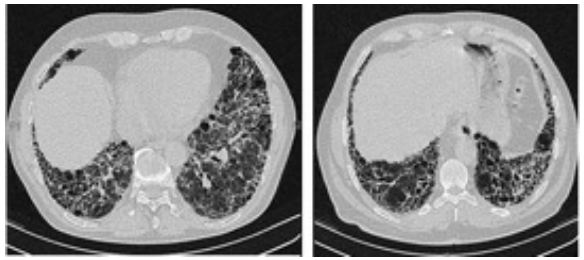


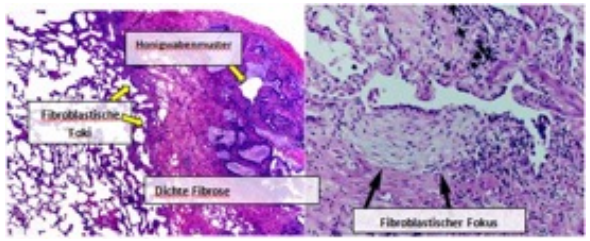
Figure S1. Mechanism of Action for 5F9 + Rituximab Anti-Tumor Synergy and 5F9 Priming/Maintenance Dose Impact on Anemia
A. Diagram showing mechanism of anti-tumor synergy combining 5F9 with rituximab. Synergy occurs through supply of an extrinsic “eat me” signal by rituximab through the Fc-Fc receptor interaction combined with blockade of the “do not eat me” CD47 signal by 5F9. B. Diagram showing the impact of a low priming dose of 5F9 eliminating only aged RBCs which express eat me signals whereas younger RBCs do not (top). The priming dose leads to a mild anemia resolved by a compensatory reticulocytosis as 5F9 shifts the pool of RBCs from old to young (middle). Higher maintenance doses can then be administered which leads to no further anemia (bottom).

Die idiopathische Lungenfibrose oder idiopathische pulmonale Fibrose (IPF) ist eine sehr schwerwiegende chronische Erkrankung mit oft tödlichem Ausgang, die durch eine stetige Abnahme der Lungenfunktion gekennzeichnet ist. Der Begriff Lungenfibrose steht für eine Vernarbung des Lungengewebes, die zu einer ständig zunehmenden Dyspnoe (Atemnot) führt. Die Fibrose hat meistens eine schlechte Prognose. Der Begriff „idiopathisch“ wird verwendet, da die Ursache der Lungenfibrose noch nicht bekannt ist. IPF tritt meistens im Erwachsenenalter zwischen 50 und 70 Jahren auf, vor allem bei aktiven oder ehemaligen Rauchern; Männer sind häufiger betroffen als Frauen.
IPF gehört zu einer großen Gruppe von etwa 200 Lungenerkrankungen, die als interstitielle Lungenerkrankungen (englisch Interstitial Lung Disease oder ILD) bezeichnet werden und einen Befall des Lungeninterstitiums aufweisen.[2] Das Interstitium, also das Bindegewebe zwischen den Lungenbläschen (Alveolen), ist hauptsächlich befallen. Dennoch befallen diese Erkrankungen häufig nicht nur das Interstitium, sondern auch Alveolen, periphere Atemwege und Gefäße. Das Lungengewebe von Personen mit IPF weist ein charakteristisches histopathologisches Muster auf, das als gewöhnliche interstitielle Pneumonie (englisch Usual Interstitial Pneumonia oder UIP) bezeichnet wird. UIP ist die histologisch bzw. detailradiologische Entsprechung der IPF. 2011 wurden neue Richtlinien für Diagnose und Management der IPF veröffentlicht. Eine deutschsprachige Fassung der internationalen Richtlinien aus dem Jahr 2013 basiert auf einer Initiative deutscher Experten unter der Schirmherrschaft der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin (DGP) und auf den Ergebnissen einer Konsensuskonferenz.
Die Diagnose der IPF setzt den Ausschluss anderer Formen einer interstitiellen Pneumonie voraus, einschließlich anderer idiopathischer interstitieller Pneumonien und interstitieller Lungenerkrankungen (ILD) im Zusammenhang mit Umweltbelastungen, Medikamenten oder systemischen Erkrankungen









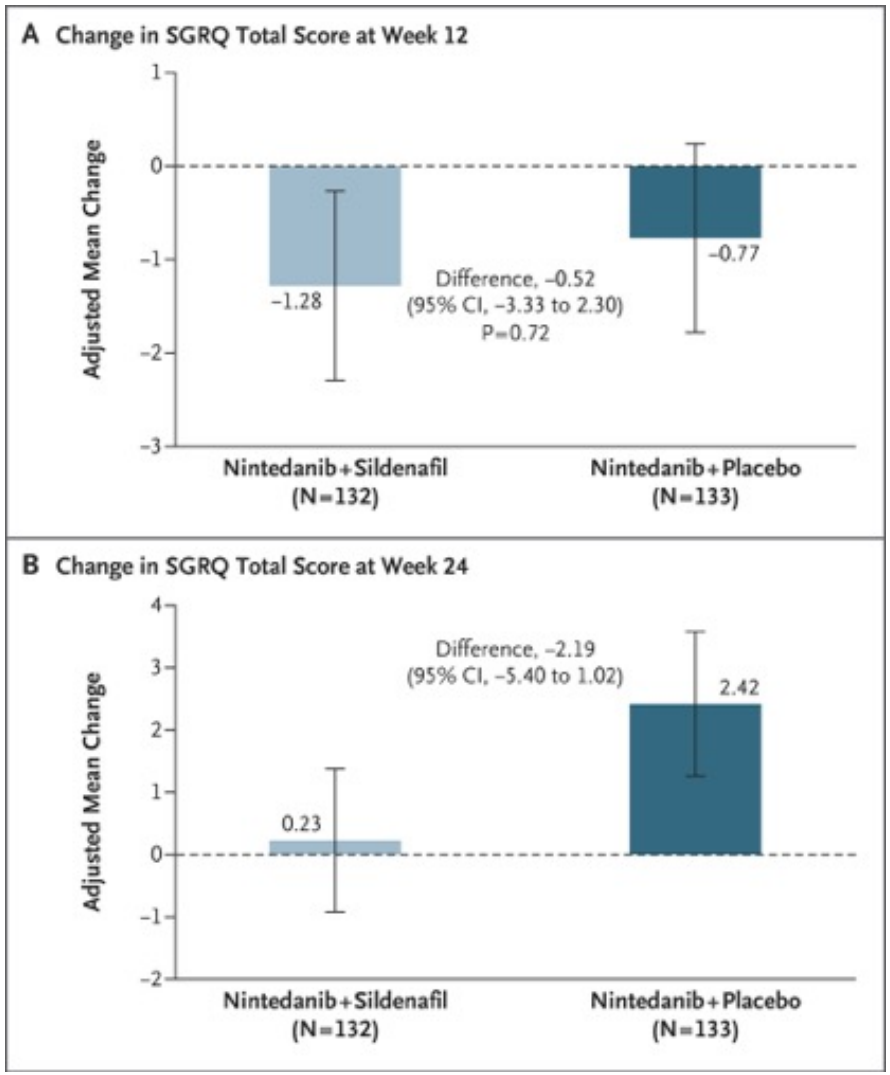
St. George ‘s Respiratory Questionnaire

Scores are calculated for three domains:
Symptoms, Activity and Impacts (Psycho-social) as well as a total score.
Psychometric testing has demonstrated its repeatability, reliability and validity. Sensitivity has been demonstrated in clinical trials.
A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing. The SGRQ has been used in a range of disease groups including asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis, and in a range of settings such as randomised controlled therapy trials and population surveys.

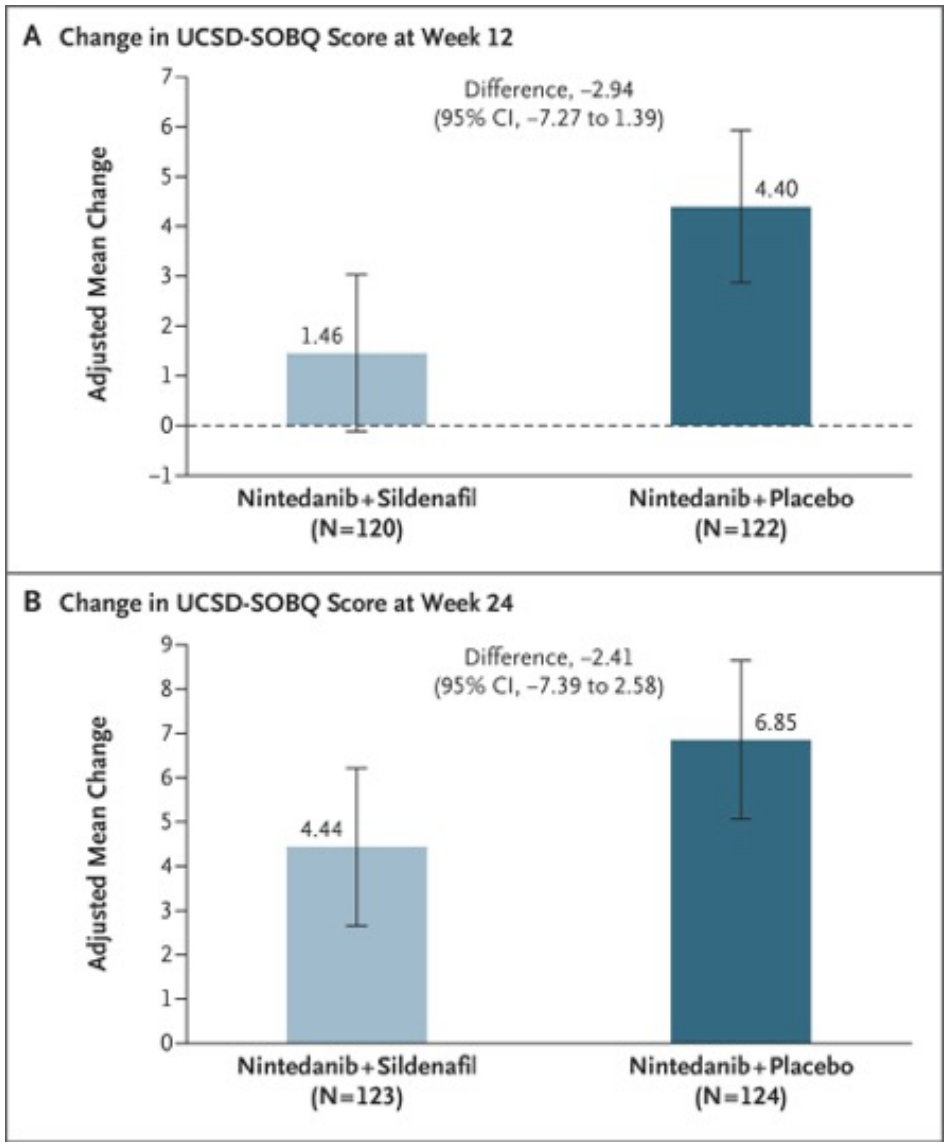
Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

Nintedanib is an approved treatment for idiopathic pulmonary fibrosis (IPF). A subgroup analysis of a previously published trial suggested that sildenafil may provide benefits regarding oxygenation, gas exchange as measured by the diffusion capacity of the lungs for carbon monoxide (DI_{CO}), symptoms, and quality of life in patients with IPF and severely decreased DI_{CO}. That idea was tested in this trial. We randomly assigned, in a 1:1 ratio, patients with IPF and a DI_{CO} of 35% or less of the predicted value to receive nintedanib at a dose of 150 mg twice daily plus sildenafil at a dose of 20 mg three times daily (nintedanib-plus-sildenafil group) or nintedanib at a dose of 150 mg twice daily plus placebo three times daily (nintedanib group) for 24 weeks. The primary end point was the change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ) at week 12 (the total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life). Secondary end points included measures of dyspnea and safety. Nintedanib, an intracellular inhibitor of tyrosine kinases,[4] is an approved treatment for IPF. Nintedanib has been shown to reduce the rate of decline in the forced vital capacity (FVC) but has had little effect on health-related quality of life as measured with the use of the St. George's Respiratory Questionnaire (SGRQ; see below).

Characteristic	Nintedanib + Sildenafil (N=137)	Nintedanib + Placebo (N=136)
Age — yr	70.3±8.6	70.0±7.9
Male sex — no. (%)	110 (80.3)	106 (77.9)
Weight — kg	73.7±17.7	74.2±15.5
Time since diagnosis of IPF — yr	2.2±1.9	2.1±1.8
Emphysema — no. (%)†	51 (37.2)	45 (33.1)
Nintedanib treatment status — no. (%)		
Not previously treated	76 (55.5)	87 (64.0)
Currently treated	56 (40.9)	46 (33.8)
Previously treated	5 (3.6)	3 (2.2)
Any echocardiographic sign indicative of right heart dysfunction — no. (%)	61 (44.5)	56 (41.2)
FVC		
Mean — ml	2246±749	2181±786
Percentage of predicted value	67.9±19.3	66.1±18.7
FEV_1:FVC	0.82±0.08	0.84±0.08
D_{LCO} — % of predicted value‡	25.8±6.8	25.6±7.0
SGRQ total score§	56.7±18.5	54.0±17.9
UCSD-SOBQ score¶	60.3±26.1	56.5±25.2
EQ-5D VAS score‖	55.8±17.9	60.0±17.8



Change from Baseline in the SGRQ Total Score at Week 12 and Week 24. The St. George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire that assesses health-related quality of life in patients with respiratory disease. The total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life. The analyses included all the patients who had at least one assessment after baseline. The I bars indicate the standard error.



Change from Baseline in the UCSD-SOBQ Score at Week 12 and Week 24. The University of California, San Diego, Shortness of Breath Questionnaire (UCSD-SOBQ) is a 24-item questionnaire assessing the severity and limitations of dyspnea during everyday activities. Scores range from 0 to 120, with higher scores indicating greater breathlessness. The I bars indicate the standard error.

Table 2. Primary, Secondary, and Further Prespecified Efficacy End Points.*

End Point	Nintedanib + Sildenafil		Nintedanib + Placebo		Difference (95% CI)
	No. of Patients	Mean Change from Baseline	No. of Patients	Mean Change from Baseline	
Assessments					
SGRQ total score					
At wk 12	120	−1.28±1.01	121	−0.77±1.0	−0.52 (−3.33 to 2.30)
At wk 24	109	0.23±1.15	105	2.42±1.16	−2.19 (−5.40 to 1.02)
UCSD-SOBQ score					
At wk 12	102	1.46±1.58	110	4.40±1.53	−2.94 (−7.27 to 1.39)
At wk 24	98	4.44±1.78	96	6.85±1.79	−2.41 (−7.39 to 2.58)
EQ-5D VAS score					
At wk 12	120	1.31±1.28	126	−2.22±1.26	3.54 (−0.02 to 7.09)
At wk 24	110	−1.48±1.56	110	−2.98±1.56	1.50 (−2.86 to 5.86)
FVC — ml					
At wk 12	119	7.0±15.9	124	−25.5±15.7	32.5 (−11.6 to 76.6)
At wk 24	109	−20.8±19.7	108	−58.2±19.6	37.4 (−17.4 to 92.3)
Rate of FVC decline — ml/24 wk†	137	−20.4±19.7	136	−66.7±19.5	46.3 (−8.3 to 100.9)
FVC — % of predicted value					
At wk 12	119	0.4±0.5	124	−0.9±0.5	1.3 (−0.1 to 2.8)
At wk 24	109	−0.5±0.6	108	−1.9±0.6	1.4 (−0.3 to 3.1)
Oxygen saturation — %					
At wk 12	121	0.20±0.27	127	0.26±0.26	−0.05 (−0.80 to 0.69)
At wk 24	113	0.03±0.32	111	−0.32±0.32	0.35 (−0.55 to 1.25)
D_{LCO} — % of predicted value					
At wk 12	114	1.3±0.7	120	−0.4±0.7	1.7 (−0.3 to 3.7)
At wk 24	105	−0.7±0.7	101	−1.6±0.7	0.9 (−1.1 to 2.9)
Brain natriuretic peptide level at wk 24 — ng/liter	108	−11.6±12.1	106	39.7±12.0	−51.3 (−85.1 to −17.6)
Time-to-event analyses	**No. of Patients**	**No. of Patients with Event (%)**	**No. of Patients**	**No. of Patients with Event (%)**	**Hazard Ratio (95% CI)**
Absolute decline of ≥5 percentage points in predicted FVC value or death	137	43 (31.4)	136	69 (50.7)	0.56 (0.38 to 0.82)
Relative decline of ≥10% in predicted FVC value or death	137	35 (25.5)	136	50 (36.8)	0.68 (0.44 to 1.05)
Relative decline of ≥15% in predicted D_{LCO} value	121	47 (38.8)	123	45 (36.6)	1.08 (0.72 to 1.64)
First investigator-reported acute exacerbation	137	10 (7.3)	136	10 (7.4)	1.00 (0.41 to 2.40)
First adjudicated confirmed or suspected acute exacerbation	137	10 (7.3)	136	10 (7.4)	0.99 (0.41 to 2.39)
Death‡					
From any cause	137	14 (10.2)	136	15 (11.0)	0.87 (0.42 to 1.81)
From any cause during treatment period	137	4 (2.9)	136	5 (3.7)	0.78 (0.21 to 2.89)
From respiratory cause	137	11 (8.0)	136	12 (8.8)	0.85 (0.37 to 1.94)

* Plus–minus values are means ±SE. The primary end point was the SGRQ total score at week 12. The numbers of patients indicate the numbers of patients who had data for the respective end point at the respective time point.
† Shown is the rate of decline (slope) in the FVC over the 24-week period in each group.
‡ Deaths from any cause were defined as deaths that occurred between randomization and last contact. Deaths during the treatment period were defined as deaths that occurred between randomization and 7 days after the end of treatment. Deaths from respiratory cause were defined as adjudicated respiratory deaths that occurred between randomization and last contact.

The adjusted mean changes from baseline in the FVC were 7.0 ml in the nintedanib-plus-sildenafil group and −25.5 ml in the nintedanib group (difference, 32.5 ml; 95% CI, −11.6 to 76.6) at week 12 and −20.8 ml and −58.2 ml, respectively (difference, 37.4 ml; 95% CI, −17.4 to 92.3), at week 24. The rate of decline in the FVC was −20.4 ml per 24 weeks in the nintedanib-plus-sildenafil group and −66.7 ml per 24 weeks in the nintedanib group (difference, 46.3 ml; 95% CI, −8.3 to 100.9).

Treatment with nintedanib plus sildenafil was associated with a lower risk of an absolute decline in the FVC of at least 5 percentage points of the predicted value or death than treatment with nintedanib alone (31.4% vs. 50.7% of patients; hazard ratio, 0.56; 95% CI, 0.38 to 0.82)

Event	Nintedanib + Sildenafil (N=137)	Nintedanib + Placebo (N=136)
	no. of patients (%)	
Any adverse event	133 (97.1)	127 (93.4)
Most frequent adverse events†		
Diarrhea	79 (57.7)	66 (48.5)
Nausea	22 (16.1)	14 (10.3)
Headache	21 (15.3)	10 (7.4)
Decreased appetite	20 (14.6)	23 (16.9)
Cough	20 (14.6)	13 (9.6)
Vomiting	19 (13.9)	10 (7.4)
Dyspnea	18 (13.1)	13 (9.6)
Severe adverse event‡	35 (25.5)	40 (29.4)
Serious adverse event§	37 (27.0)	44 (32.4)
Fatal adverse event	12 (8.8)	13 (9.6)
Adverse event leading to premature discontinuation of nintedanib only	2 (1.5)	3 (2.2)
Adverse event leading to premature discontinuation of sildenafil or placebo only	6 (4.4)	2 (1.5)
Adverse event leading to premature discontinuation of nintedanib plus either sildenafil or placebo	19 (13.9)	23 (16.9)
Major adverse cardiovascular event¶	4 (2.9)	6 (4.4)

Diarrhea was the most frequent adverse event and was reported in 57.7% of the patients in the nintedanib-plus-sildenafil group and in 48.5% of those in the nintedanib group. The percentage of patients with a serious adverse event was 27.0% in the nintedanib-plus-sildenafil group and 32.4% in the nintedanib group (relative risk, 0.83; 95% CI, 0.58 to 1.20; risk difference, −5.4 percentage points; 95% CI, −16.2 to 5.5). Elevations in the alanine aminotransferase level, the aspartate aminotransferase level, or both to at least 3 times the upper limit of the normal range were reported in 8 patients (5.8%) in the nintedanib-plus-sildenafil group and in 12 (8.8%) in the nintedanib group.

The results of the previously published trial STEP-IPF indicated that sildenafil may provide benefits regarding DI_{CO}, oxygenation, symptoms, and health-related quality of life in patients with IPF and severely impaired gas exchange. That led us to design and carry out the INSTAGE trial, in which a combination of sildenafil and the approved antifibrotic drug nintedanib was tested against nintedanib alone. We found that the addition of sildenafil to nintedanib was not associated with greater benefits than nintedanib alone, regarding health-related quality of life as measured by means of the SGRQ, UCSD-SOBQ, or EQ-5D visual-analogue scale over a period of 24 weeks. The strengths of our analyses include the prespecification of all the reported end points and the minimal amount of missing data. Limitations include the potential underpowering of the trial and its relatively short duration. The side-effect data should be interpreted in light of the observation that more than one third of the patients had received nintedanib before entering the trial and so would have been likely to have had fewer adverse events than a population of patients who had never received nintedanib previously. The lack of a trial group that received only placebo prevents firm conclusions from being drawn regarding the efficacy and safety of nintedanib monotherapy in this population of patients. All the patient-reported outcomes that were used to measure health-related quality of life in patients with IPF have limitations and were not developed in patients with IPF.

Changes in Prevalence of Health Care–Associated Infections in U.S. Hospitals

A point-prevalence survey that was conducted in the United States in 2011 showed that 4% of hospitalized patients had a health care–associated infection. We repeated the survey in 2015 to assess changes in the prevalence of health care–associated infections during a period of national attention to the prevention of such infections. At Emerging Infections Program sites in 10 states, we recruited up to 25 hospitals in each site area, prioritizing hospitals that had participated in the 2011 survey. Each hospital selected 1 day on which a random sample of patients was identified for assessment. Trained staff reviewed medical records using the 2011 definitions of health care–associated infections. We compared the percentages of patients with health care–associated infections and performed multivariable log-binomial regression modeling to evaluate the association of survey year with the risk of health care–associated infections.

Characteristic	All Patients (N = 12,299)	Patients without Health Care–Associated Infection (N = 11,905)	Patients with Health Care–Associated Infection (N = 394)	P Value†
Hospital size — no. (%)‡				<0.001
Small	3,975 (32.3)	3,889 (32.7)	86 (21.8)	
Medium	5,629 (45.8)	5,459 (45.9)	170 (43.1)	
Large	2,695 (21.9)	2,557 (21.5)	138 (35.0)	
Location of patient in hospital on survey date — no. (%)				<0.001
Critical care unit	1,834 (14.9)	1,719 (14.4)	115 (29.2)	
Unit housing patients receiving different levels of acute care	228 (1.9)	220 (1.8)	8 (2.0)	
Newborn or special care nursery	456 (3.7)	455 (3.8)	1 (0.3)	
Specialty care area	60 (0.5)	58 (0.5)	2 (0.5)	
Step-down unit	547 (4.4)	525 (4.4)	22 (5.6)	
Ward, excluding nursery	9,174 (74.6)	8,928 (75.0)	246 (62.4)	
Central catheter in place on survey date — no. (%)				<0.001
Any	2,081 (16.9)	1,868 (15.7)	213 (54.1)	
One catheter	1,716 (14.0)	1,542 (13.0)	174 (44.2)	
More than one catheter	217 (1.8)	188 (1.6)	29 (7.4)	
Unknown number of catheters	148 (1.2)	138 (1.2)	10 (2.5)	
None	10,175 (82.7)	9,995 (84.0)	180 (45.7)	
Missing data	43 (0.3)	42 (0.4)	1 (0.3)	
Urinary catheter in place on survey date — no. (%)				<0.001
Yes	2,299 (18.7)	2,164 (18.2)	135 (34.3)	
No	9,959 (81.0)	9,703 (81.5)	256 (65.0)	
Missing data	41 (0.3)	38 (0.3)	3 (0.8)	
Ventilator in place on survey date — no. (%)				<0.001
Yes	586 (4.8)	505 (4.2)	81 (20.6)	
No	11,683 (95.0)	11,371 (95.5)	312 (79.2)	
Missing data	30 (0.2)	29 (0.2)	1 (0.3)	
Receiving or scheduled to receive antimicrobial therapy on the survey date or day before the survey, or information not available — no. (%)	6,223 (50.6)	5,829 (49.0)	NA§	—
Median no. of days from admission to survey (IQR)	3 (1–6)	2 (1–6)	13 (7–21)	<0.001¶
Median hospital length of stay (IQR) — days	5 (3–11)	5 (3–10)‖	20 (11–37)**	<0.001¶

Table 2. Comparison of Selected Characteristics of the Patients, 2011 vs. 2015 Survey.*

Characteristic	2011 Survey Patients (N=11,282)	2015 Survey Patients (N=12,299)	P Value†
Survey month — no. (%)			<0.001
May or June	5863 (52.0)	3008 (24.5)	
July, August, or September	5419 (48.0)	9291 (75.5)	
Hospital size — no. (%)			<0.001
Small	4073 (36.1)	3975 (32.3)	
Medium	4995 (44.3)	5629 (45.8)	
Large	2214 (19.6)	2695 (21.9)	
Location of patient in hospital on survey date — no. (%)‡			<0.001
Critical care unit	1707 (15.1)	1834 (14.9)	
Unit housing patients receiving different levels of acute care	119 (1.1)	228 (1.9)	
Newborn or special care nursery	485 (4.3)	456 (3.7)	
Specialty care area	49 (0.4)	60 (0.5)	
Step-down unit	466 (4.1)	547 (4.4)	
Ward, excluding nursery	8456 (75.0)	9174 (74.6)	
Central catheter in place on survey date — no. (%)			<0.001
Yes	2121 (18.8)	2081 (16.9)	
No	9140 (81.0)	10,175 (82.7)	
Missing data	21 (0.2)	43 (0.3)	
Urinary catheter in place on survey date — no. (%)			<0.001
Yes	2659 (23.6)	2299 (18.7)	
No	8594 (76.2)	9959 (81.0)	
Missing data	29 (0.3)	41 (0.3)	
Received or were scheduled to receive antimicrobial therapy on the survey date or day before the survey, or information not available — no. (%)	5849 (51.8)§	6223 (50.6)	0.06
Received antimicrobial therapy for infection treatment or no documented rationale at time of survey — no. (%)	4504 (39.9)¶	4614 (37.5)	<0.001
Median no. of days from admission to survey (IQR)	3 (1–6)	3 (1–6)	0.40‖
Outcome among patients with health care–associated infection only — no./total no. (%)			0.99**
Survived	386/452 (85.4)	348/394 (88.3)	
Died	50/452 (11.1)	45/394 (11.4)	
Still in hospital or data were missing	16/452 (3.5)	1/394 (0.3)	

* Percentages may not total 100 because of rounding.
† The chi-square test was used for calculating the P value, unless otherwise indicated. The comparison excluded patients with missing data, unless otherwise indicated.
‡ The locations of the patients were defined according to the 2015 National Healthcare Safety Network categories. Solid-organ transplantation and dialysis units were classified as specialty care areas, and bone marrow transplantation and hematology–oncology units were classified as non–nursery ward locations.
§ The analysis excluded 11 patients in the 2011 survey who were screen-positive based on a special criterion for dialysis patients. This criterion was not implemented in the 2015 survey.
¶ The analysis included 7 patients who underwent medical record review for health care–associated infection because they met the antimicrobial use screening criterion for patients undergoing dialysis. This criterion was not implemented in the 2015 survey.
‖ The P value was calculated by a median two-sample test. The number of days from admission to survey was calculated by subtracting the admission date from the survey date.
** The comparison included only patients for whom the outcome was known (died vs. survived).

In both surveys, approximately 15% of the patients were in critical care units, the median time from admission to the survey date was 3 days, and approximately 11% of patients with a health care–associated infection died during their hospitalization. The percentages of patients with a urinary catheter or central catheter (known as a central line in surveillance of the National Healthcare Safety Network) on the survey date were lower in 2015 (urinary catheter, 18.7%; central catheter, 16.9%) than in 2011 (urinary catheter, 23.6%; central catheter, 18.8%) (P<0.001 for both comparisons).

In the 2015 survey, 4614 patients (37.5%) met the criterion for review of health care–associated infection by receiving antimicrobial agents for the treatment of an infection or receiving antimicrobial agents for which the rationale was not documented. This percentage was lower than that of patients who met the same review criterion in the 2011 survey (39.9%, P<0.001).

Applying the same definitions of health care–associated infections that had been used in 2011, we found that 394 of 12,299 patients in the 2015 survey had one or more health care–associated infections (3.2%; 95% confidence interval [CI], 2.9 to 3.5), as compared with 452 of 11,282 patients (4.0%; 95% CI, 3.7 to 4.4) in the 2011 survey (P<0.001).

Table 3. Multivariable Log-Binomial Regression Model to Identify Variables Associated with Health Care–Associated Infections, Combined 2011 and 2015 Survey Populations.*

Variable	Total No. of Patients	No. of Patients with Infection	Adjusted Risk Ratio (95% CI)	P Value
Survey year 2015†	12,299	394	0.84 (0.74–0.95)	0.005
Ventilator on the survey date‡	1,113	176	1.63 (1.38–1.92)	<0.001
Central catheter on the survey date§	4,202	472	1.84 (1.59–2.13)	<0.001
Urinary catheter on the survey date¶	4,958	312	1.24 (1.07–1.44)	0.004
Large hospital‖	4,909	280	1.20 (1.05–1.37)	0.007
Time from admission to survey				
≤1 day	7,022	27	Reference	—
2–4 days	9,013	81	2.15 (1.41–3.38)	<0.001
5–6 days	2,154	76	7.14 (4.67–11.26)	<0.001
7–9 days	1,834	127	12.97 (8.71–20.05)	<0.001
≥10 days	3,557	535	25.45 (17.54–38.58)	<0.001
Age**				
<40 yr	7,217	172	Reference	—
40–50 yr	2,185	88	1.50 (1.17–1.89)	<0.001
51–57 yr	2,277	114	1.67 (1.33–2.08)	<0.001
58–65 yr	3,048	140	1.45 (1.17–1.78)	<0.001
66–72 yr	2,703	104	1.39 (1.10–1.75)	0.005
73–80 yr	2,815	113	1.56 (1.24–1.95)	<0.001
≥81 yr	3,335	115	1.65 (1.31–2.07)	<0.001

* The total number of patients who were included in either survey was 23,581. One patient from the 2011 survey for whom age was unknown was excluded from the model. Other variables that were tested but found not to be significant predictors of the risk of health care–associated infection were survey month (May or June vs. July through September) and location of the patient in a critical care unit (yes vs. no).

† The comparator group for the risk ratio was the group of patients in the 2011 survey.

‡ The comparator group for the risk ratio was the group of patients without a ventilator or for whom the presence of a ventilator was unknown. The presence of a ventilator was unknown for 36 patients without a health care–associated infection and for 1 with a health care–associated infection.

§ The comparator group for the risk ratio was the group of patients without a central catheter or for whom the presence of a central catheter was unknown. The presence of a central catheter was unknown for 62 patients without a health care–associated infection and for 2 with a health care–associated infection.

¶ The comparator group for the risk ratio was the group of patients without a urinary catheter or for whom the presence of a urinary catheter was unknown. The presence of a urinary catheter was unknown for 65 patients without a health care–associated infection and for 5 with a health care–associated infection.

‖ The comparator group for the risk ratio was the group of patients in small or medium hospitals.

** The model excluded 1 patient without a health care–associated infection for whom age was unknown.

After adjustment for age, time from admission to survey, presence of devices, and status of being in a large hospital, patients in the 2015 survey were 16% less likely to have a health care–associated infection than patients in the 2011 survey (risk ratio, 0.84; 95% CI, 0.74 to 0.95; P=0.005). We repeated the analysis in the subgroup of patients who met the review criterion. After adjustment for similar factors, patients in the 2015 survey remained less likely than those in the 2011 survey to have a health care–associated infection (risk ratio, 0.84; 95% CI, 0.75 to 0.94; P=0.003). Results were similar in an analysis that was restricted to 148 hospitals that participated in both surveys. In these hospitals, the percentage of patients with a health care–associated infection was 3.2% (95% CI, 2.9 to 3.6) in 2015 (297 of 9169 patients), as compared with 4.1% (95% CI, 3.7 to 4.6) in 2011 (383 of 9283 patients) (P=0.001).

Table 4. Percentages of All Surveyed Patients with Specific Types of Health Care–Associated Infection, 2011 vs. 2015 Survey.*

Type of Infection	2011 Survey			2015 Survey			P Value†
	No. of Patients with Infection	No. of Infections	Percentage of Patients with Infection (95% CI)	No. of Patients with Infection	No. of Infections	Percentage of Patients with Infection (95% CI)	
Pneumonia	110	110	0.98 (0.81–1.20)	110	110	0.89 (0.74–1.10)	0.52
Ventilator-associated pneumonia	43	43	0.38 (0.28–0.51)	39	39	0.32 (0.23–0.43)	0.41
Other pneumonia	67	67	0.59 (0.47–0.75)	71	71	0.58 (0.46–0.73)	0.87
Gastrointestinal infection	86	86	0.76 (0.62–0.94)	91	91	0.74 (0.60–0.91)	0.84
Clostridium difficile infection‡	61	61	0.54 (0.42–0.69)	66	66	0.54 (0.42–0.68)	0.97
Other gastrointestinal infection	25	25	0.22 (0.15–0.33)	25	25	0.20 (0.14–0.30)	0.76
Surgical-site infection	109	110	0.97 (0.80–1.20)	69	69	0.56 (0.44–0.71)	<0.001
Deep incisional or organ-space infection	77	77	0.68 (0.55–0.85)	54	54	0.44 (0.34–0.57)	0.01
Superficial incisional infection	33	33	0.29 (0.21–0.41)	15	15	0.12 (0.07–0.20)	0.004
Bloodstream infection	50	50	0.44 (0.34–0.58)	51	52	0.41 (0.31–0.55)	0.74
Central catheter–associated bloodstream infection	42	42	0.37 (0.27–0.50)	37	38	0.30 (0.22–0.42)	0.35
Other primary bloodstream infection	8	8	0.07 (0.03–0.14)	14	14	0.11 (0.07–0.19)	0.29
Urinary tract infection	65	65	0.58 (0.45–0.73)	39	39	0.32 (0.23–0.43)	0.003
Catheter-associated urinary tract infection	44	44	0.39 (0.29–0.52)	24	24	0.20 (0.13–0.29)	0.005
Other urinary tract infection	21	21	0.19 (0.12–0.29)	15	15	0.12 (0.07–0.20)	0.21
Other infection§	78	83	0.69 (0.55–0.86)	61	66	0.50 (0.39–0.64)	0.05
Any infection	452	504	4.0 (3.7–4.4)	394	427	3.2 (2.9–3.5)	<0.001

* A total of 11,282 patients were included in the 2011 survey, and 12,299 in the 2015 survey; these values are the denominators for the percentages of patients with infection. Patients could have more than one health care–associated infection.

† P values were calculated by a mid-P exact test.

‡ *Clostridium difficile* is now known as *Clostridioides difficile*.

§ Other infections in the 2011 survey included the following: ear, eye, nose, and throat infections (28 infections); lower respiratory tract infection (20); skin and soft-tissue infections (16); cardiovascular infection (6); bone and joint infections (5); central nervous system infection (4); reproductive tract infection (3); and systemic infection (1). Other infections in the 2015 survey included the following: skin and soft-tissue infections (22 infections); ear, eye, nose, and throat infections (21); lower respiratory tract infection (18); bone and joint infections (2); central nervous system infection (1); cardiovascular infection (1); and reproductive tract infection (1).

Table 5. Pathogens Reported for Health Care–Associated Infections, 2015.*

Pathogen	All Infections (N = 427)	Pneumonia (N = 110)†	Gastrointestinal Infection (N = 91)‡	Surgical-Site Infection (N = 69)§	Bloodstream Infection (N = 52)¶	Urinary Tract Infection (N = 39)‖	Other Infection (N = 66)**
	number of infections (percent)						
C. difficile	66 (15)	0	66 (73)	0	0	0	0
Staphylococcus aureus	48 (11)	13 (12)	2 (2)	12 (17)	12 (23)	0	9 (14)
Escherichia coli	44 (10)	2 (2)	1 (1)	13 (19)	4 (8)	18 (46)	6 (9)
Candida species	26 (6)	7 (6)	3 (3)	1 (1)	7 (13)	3 (8)	5 (8)
Enterococcus species	23 (5)	1 (1)	2 (2)	8 (12)	6 (12)	4 (10)	2 (3)
Enterobacter species††	22 (5)	3 (3)	1 (1)	10 (14)	0	3 (8)	5 (8)
Pseudomonas aeruginosa	22 (5)	8 (7)	2 (2)	3 (4)	0	5 (13)	4 (6)
Klebsiella pneumoniae or *K. oxytoca*	21 (5)	6 (5)	1 (1)	3 (4)	3 (6)	7 (18)	1 (2)
Streptococcus species‡‡	21 (5)	4 (4)	1 (1)	9 (13)	6 (12)	0	1 (2)
Coagulase-negative staphylococcus	16 (4)	1 (1)	2 (2)	6 (9)	6 (12)	0	1 (2)
Other gram-negative bacterium§§	11 (3)	2 (2)	0	4 (6)	1 (2)	1 (3)	3 (5)
Proteus mirabilis	8 (2)	0	0	3 (4)	1 (2)	3 (8)	1 (2)
Other gram-positive bacterium¶¶	8 (2)	0	0	6 (9)	1 (2)	0	1 (2)
Stenotrophomonas species	6 (1)	1 (1)	1 (1)	0	2 (4)	0	2 (3)
Acinetobacter baumannii	6 (1)	1 (1)	0	0	2 (4)	0	3 (5)
Bacteroides species‖	5 (1)	0	0	2 (3)	3 (6)	0	0
Virus***	5 (1)	1 (1)	0	0	0	0	4 (6)
Citrobacter freundii	4 (1)	0	0	1 (1)	1 (2)	1 (3)	1 (2)
Prevotella species	4 (1)	0	0	3 (4)	1 (2)	0	0
Serratia species	4 (1)	3 (3)	0	1 (1)	0	0	0
Mold	4 (1)	1 (1)	0	1 (1)	0	0	2 (3)
Yeast, not otherwise specified	4 (1)	3 (3)	0	0	1 (2)	0	0
Haemophilus influenzae, type not specified	3 (1)	3 (3)	0	0	0	0	0
Lactobacillus species	3 (1)	1 (1)	0	1 (1)	0	0	1 (2)
Other pathogen†††	2 (<1)	1 (1)	1 (1)	0	0	0	0
No pathogen reported	127 (30)	64 (58)	16 (18)	19 (28)	0	0	28 (42)

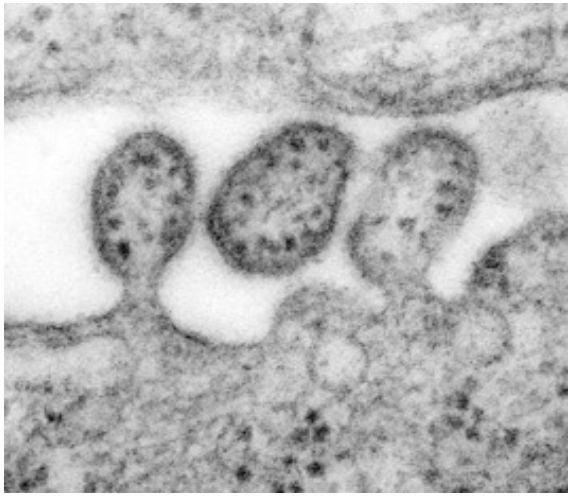
* Pathogens were reported for 300 of 427 health care–associated infections. Up to 3 pathogens could be reported for each infection.
† A total of 62 pathogens were reported for 46 of 110 pneumonias (42%).
‡ A total of 83 pathogens were reported for 75 of 91 gastrointestinal infections (82%).
§ A total of 89 pathogens were reported for 50 of 69 surgical-site infections (72%). Two organisms in the same genus or pathogen group were reported for each of 2 surgical-site infections.
¶ A total of 59 pathogens were reported for 52 of 52 bloodstream infections (100%). The definition of a bloodstream infection required pathogen reporting. Two organisms in the same genus were reported for each of 2 bloodstream infections (2 streptococcus species were reported for 1 bloodstream infection, and 2 bacteroides species were reported for another bloodstream infection).
‖ A total of 45 pathogens were reported for 39 of 39 urinary tract infections (100%). The definition of a urinary tract infection required pathogen reporting.
** A total of 54 pathogens were reported for 38 of 66 other infections (58%). Two organisms in the same genus were reported for each of 2 other infections.
†† A total of 23 enterobacter were reported for 22 health care–associated infections (*E. cloacae* and *E. aerogenes* [now *Klebsiella aerogenes*] were each reported for 1 infection).
‡‡ A total of 24 streptococci were reported for 21 health care–associated infections (2 different streptococci were reported for each of 3 infections).
§§ Pathogens included gram-negative rod (not otherwise specified; for 2 infections), *Morganella morganii* (for 2), *Burkholderia cepacia* (for 1), capnocytophaga species (for 1), *Chryseomonas luteola* (now *Pseudomonas luteola*; for 1), *Eikenella corrodens* (for 1), gram-negative coccus (not otherwise specified; for 1), *Legionella pneumophila* (for 1), and neisseria species (for 1).
¶¶ Pathogens included 9 other gram-positive bacteria for 8 health care–associated infections: gram-positive coccus (not otherwise specified; for 3 infections), corynebacterium species (for 2), gram-positive rod (not otherwise specified; for 2), *Clostridium perfringens* (for 1), and *Rothia mucilaginosa* (for 1).
‖ A total of 6 bacteroides were reported for 5 health care–associated infections (both *B. fragilis* and *B. thetaiotaomicron* were reported for 1 infection).
*** Pathogens included rhinovirus (for 3 infections), cytomegalovirus (for 1), and herpes simplex virus type 2 (for 1).
††† Pathogens included *Pneumocystis jirovecii* (for 1 infection) and other unspecified pathogen (for 1).

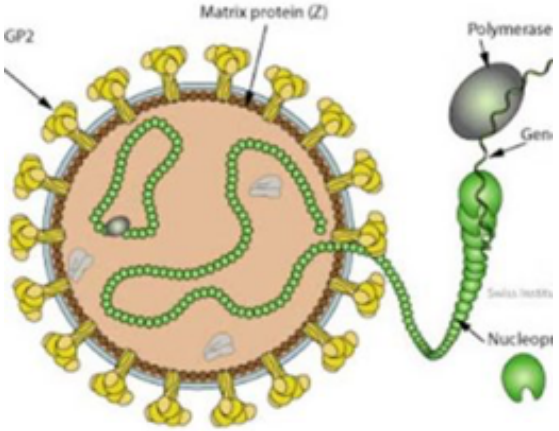
In this point-prevalence survey conducted in multiple states, we found that health care–associated infections affected 3.2% of hospitalized patients — a significantly lower percentage than we observed in a survey that had been conducted in 2011. These results provide evidence of national success in preventing health care–associated infections, particularly surgical-site and urinary tract infections. In contrast, there was no significant reduction in the prevalence of pneumonia or *C. difficile* infection, nor in the percentage of patients with health care–associated infection who died during their hospitalization, which suggests that more work is needed to prevent these infection types and reduce mortality among patients with health care–associated infections.

Although the prevalence of health care–associated infections was significantly lower in 2015 than in 2011, we did not directly compare the national burden estimates from the two surveys. Two barriers to such a comparison were present. First, there were differences in the variables that remained in the best-fitting multivariable regression models that were used in the 2011 and 2015 burden-estimation processes. For example, we lacked complete data regarding the length of stay in the hospital for patients in the 2011 survey and therefore used a proxy measure (the number of days from admission to the survey). In addition, the Nationwide Inpatient Sample underwent a redesign starting with 2012 data and was renamed the National Inpatient Sample.

Prevalence surveys capture the range and relative frequencies of all health care–associated infections among hospitalized patients and complement ongoing tracking of these infections. The health care–associated infections that we identified in this survey are only one portion of the overall burden of such infections, which includes infections that occur in other settings, such as nursing homes. The CDC and the Emerging Infections Program sites are collaborating on a large-scale nursing home prevalence survey to address this gap.[31] Collaborations among health care facilities, public health agencies, and other partners, bolstered by recent increases in support for programs regarding health care–associated infections, will be critical to the continued progress toward the goal of eliminating health care–associated infections.

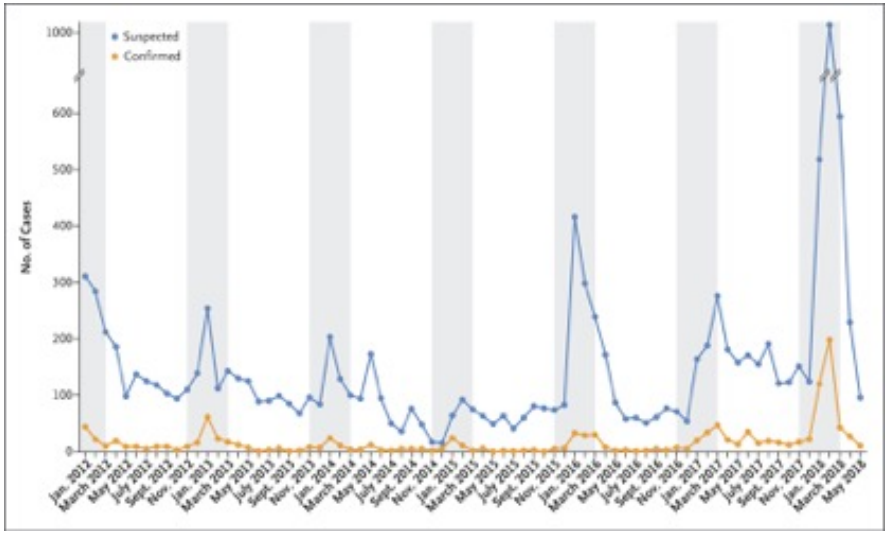
Das Lassafieber ist eine meldepflichtige Erkrankung und gehört wie das Marburgfieber zu den viralen hämorrhagischen Fiebern. Das Lassafieber wurde 1969 zum ersten Mal beschrieben. Zu dieser Zeit starb in Nigeria eine amerikanische Missionsschwester, eine weitere erkrankte und wurde zur Behandlung in die USAausgeflogen.
Das Virus wurde nach der Stadt Lassa im heutigen Bundesstaat Borno benannt, in der die erste Krankenschwester gearbeitet hatte. In New York City traten unter Wissenschaftlern, die das Virus isolierten, zwei Laborinfektionen auf, einer der Infizierten verstarb infolge der Erkrankung. Der Verursacher des Lassa-Fiebers ist ein behülltes einzel(–)-Strang-RNA-Virus = ss(–)RNA mit hoher Virulenz und gehört zu Gattung Arena-Virus und damit zur Familie Arenaviridae. Zur selben Virenfamilie gehören auch die Erreger des Juninfiebers und des Machupofiebers. Sie alle werden der höchsten biologischen Sicherheitsstufe 4 zugeordnet. Vom Lassa-Virus sind bisher vier serologische Subtypen bekannt: Typ Nigeria, Sierra Leone, Liberia und Typ Zentralafrikanische Republik.
Die relativ hohe Sterblichkeit der durch diese Viren ausgelösten Erkrankung deutet darauf hin, dass die Lassa-Viren noch nicht besonders stark an den Menschen angepasst sind. Ein an seinen Wirt angepasstes Virus hat kein Interesse im Sinne eines Selektionsdrucks daran, ihn zu zerstören, denn es braucht ihn für seine Vermehrung. Serologische Daten lassen jedoch vermuten, dass zumindest in Westafrika etwa 90 bis 95 % aller Infektionen ohne Krankheitsausbruch verlaufen könnten. Das würde bedeuten, dass regional begrenzt bei den einheimischen Menschen im natürlichen Verbreitungsgebiet des Virus eine Anpassung des Menschen oder der Viren schon stattgefunden hat. Als natürlicher Reservoirwirt für das Lassa-Virus ist neben anderen Kleinnagern hauptsächlich die Natal-Vielzitzenmaus (Mastomys natalensis) festgestellt worden.





Genomic Analysis of Lassa Virus during an Increase in Cases in Nigeria in 2018

During 2018, an unusual increase in Lassa fever cases occurred in Nigeria, raising concern among national and international public health agencies. We analyzed 220 Lassa virus genomes from infected patients, including 129 from the 2017–2018 transmission season, to understand the viral populations underpinning the increase. A total of 14 initial genomes from 2018 samples were generated at Redeemer's University in Nigeria, and the findings were shared with the Nigerian Center for Disease Control in real time. We found that the increase in cases was not attributable to a particular Lassa virus strain or sustained by human-to-human transmission. Instead, the data were consistent with ongoing cross-species transmission from local rodent populations. Phylogenetic analysis also revealed extensive viral diversity that was structured according to geography, with major rivers appearing to act as barriers to migration of the rodent reservoir.

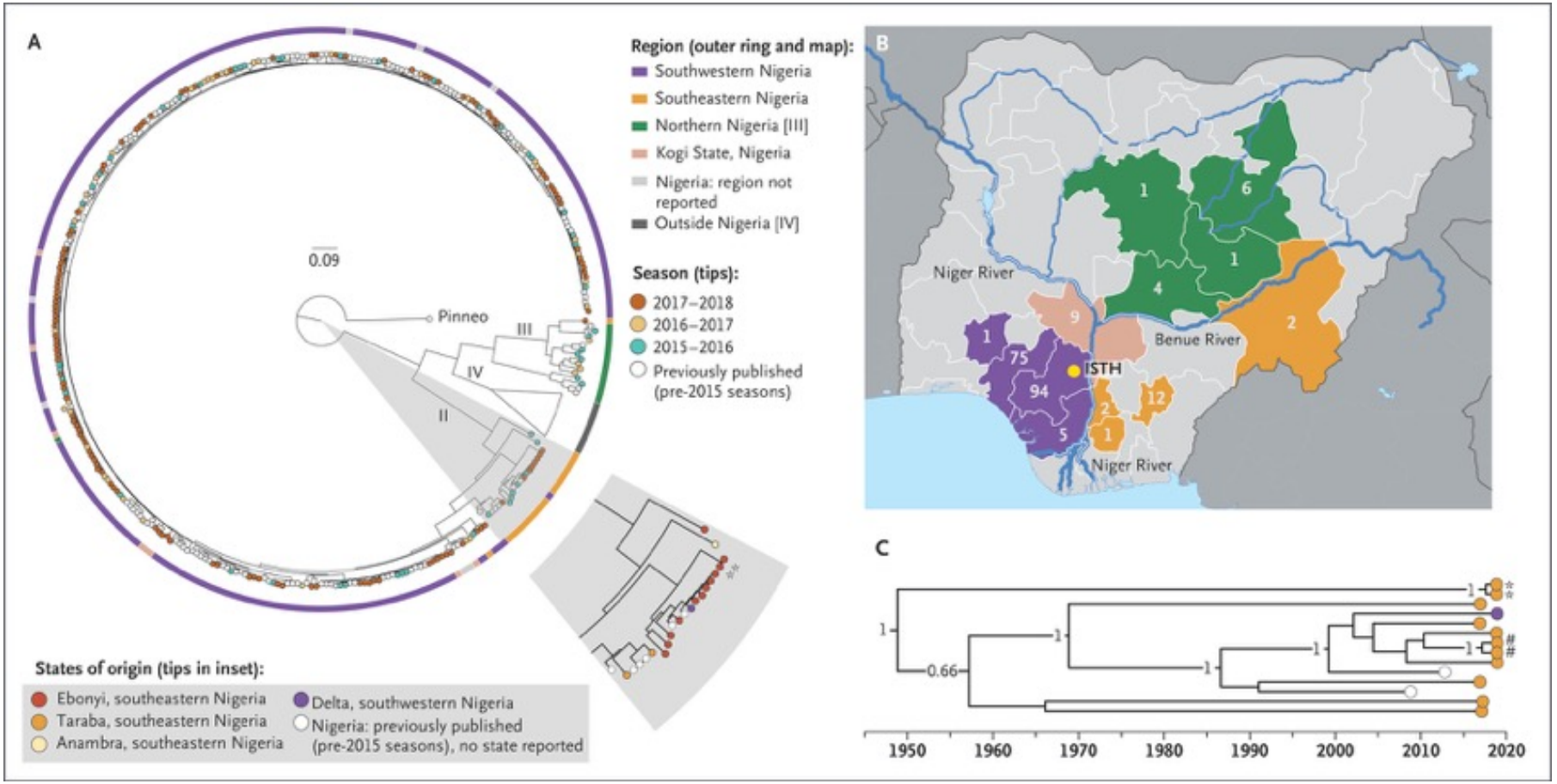


. Lassa Fever Cases over Time. The numbers of clinically suspected and confirmed (reverse-transcriptase quantitative polymerase-chain-reaction–positive) cases of Lassa fever identified at the Irrua Specialist Teaching Hospital are shown for each month from January 2012 through May 2018. Gray shading indicates the typical dry season in Edo State, Nigeria, which overlaps with the period of peak Lassa fever incidence.

Table 1. Sequencing Metrics in Each Lassa Virus Season from 2015 through 2018.*

Season and Laboratory	No. of Genomes	Assembly Length	Mean Coverage (Range)
		bp	
2017–2018			
ACEGID	14	10,258	207× (1–1,834)
ACEGID or Broad Institute	115	9,959	586× (4–12,822)
2016–2017			
Broad Institute	39	10,495	604× (12–4,801)
2015–2016			
ACEGID or Broad Institute	52	10,374	1,531× (12–10,195)
Total	220		

* Samples were sequenced at the African Center of Excellence for Genomics of Infectious Diseases (ACEGID), Redeemer's University, on an Illumina MiSeq or at the Broad Institute on an Illumina HiSeq2500 or NovaSeq. To confirm the reproducibility of the assemblies, 14 samples were sequenced at both sites, resulting in 220 unique genomes.



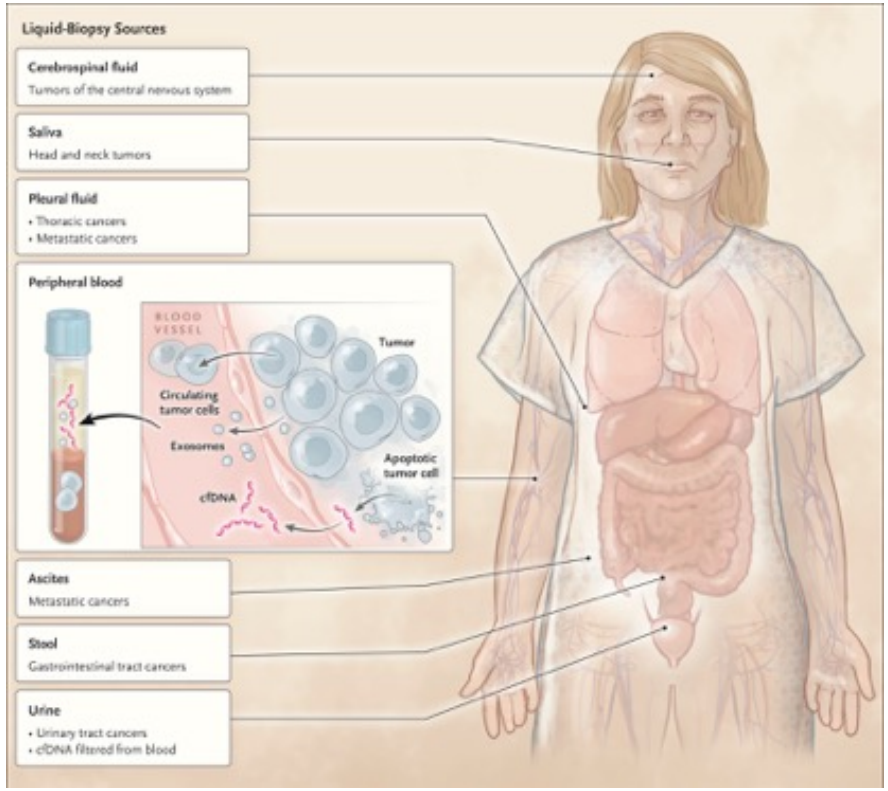
Distribution of Lassa Virus Genetic Diversity in Nigeria. Panel A shows a maximum-likelihood phylogenetic tree of the S segment of the Lassa virus genome. The tree incorporates the genomes reported here from 2015 through 2018, along with 193 previously published genomes from Nigeria and the Mano River Union (the latter belong to lineage IV and are depicted as a single triangle). The new samples are colored according to the season in which they were obtained; the outer ring indicates the geographic regions in which the patients reside. (For samples that were obtained before 2015 and for which geographic region is not known, the geographic region is assumed on the basis of its location in the tree.) The inset shows part of lineage II, in which known nosocomial transmissions are indicated with asterisks. (An apparent human-to-human transmission chain in the inset is not supported by time-aware phylogeny analysis: the times to the most recent common ancestor in the chain are between 10 and 20 years.) Panel B shows a map of Nigeria in which the numbers of new genomes are indicated for each state; for seven samples, the state was unknown. Colors are the same as those used in the outer ring in Panel A. We were unable to confirm fine-scale geographic locations of the samples originating from Kogi State, although all samples clustered within the southwestern sublineage of lineage II. Panel C shows a time-aware phylogeny of the part of lineage II that is shown in the inset in Panel A. Patients who acquired the infection from a known nosocomial transmission event are indicated with an asterisk, and two possible but unconfirmed transmissions are indicated with number signs.

We investigated the genomic diversity of Lassa virus in humans to better understand the increase in Lassa fever cases that occurred in 2018 in Nigeria. In a data set of 220 genomes, including 129 from 2018, we found no evidence that a particular viral strain or extensive human-to-human transmission drove the increase. In particular, Lassa virus in 2018 was drawn from a wide range of previously observed viral diversity rather than from a single dominant strain, and we did not find extensive phylogenetic clustering of Lassa virus from samples that had been collected close together in time, as would be expected if this increase were driven by human-to-human transmission. The absence of these patterns suggests that Lassa virus transmission in 2018 continues to be sustained largely by numerous distinct cross-species transmission events from a genetically diverse reservoir. These findings helped to guide the public health response by alleviating concerns about a new or more virulent strain of Lassa virus, perhaps with a higher potential for human-to-human transmission, as a potential explanation for the increase in cases. The reason for the unusual increase in Lassa fever cases remains unknown, but it may involve changes in the rodent reservoir population or improved surveillance and heightened public awareness. These data help resolve the geographic structure and recent population history of Lassa virus in Nigeria. For example, the most recent common ancestor in the viral population west of the Niger River is substantially younger than that east of the river (with estimated times to the most recent common ancestor of 74 and 219 years, respectively), which suggests that either the introduction of the virus or a population bottleneck occurred in the western areas within the past century. The persistent segregation of these two populations since that time suggests the importance of established local rodent populations in sustaining distinct viral populations.[16] Broader geographic sampling of Lassa virus, including from the poorly characterized rodent reservoir, is needed to fully understand viral diversity and may be useful for the development of diagnostics, therapeutics, and vaccines.

Application of Cell-free DNA Analysis to Cancer Treatment

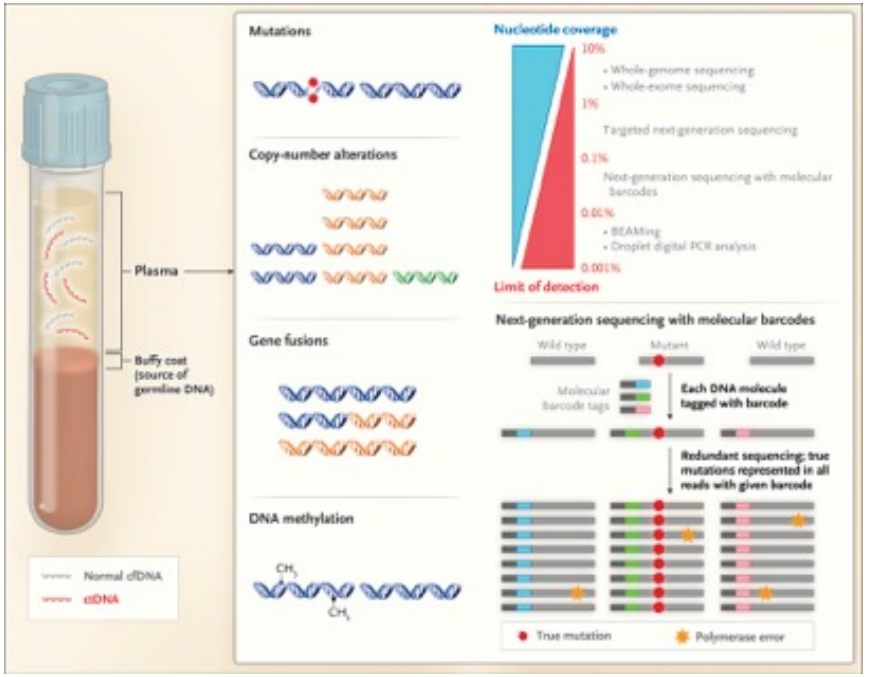
Tumor biopsies represent the standard for cancer diagnosis and the primary method for molecular testing to guide the selection of precision therapies. Liquid biopsies, particularly those involving cell-free DNA (cfDNA) from plasma, are rapidly emerging as an important and minimally invasive adjunct to standard tumor biopsies and, in some cases, even a potential alternative approach. Liquid biopsy is becoming a valuable tool for molecular testing, for new insights into tumor heterogeneity, and for cancer detection and monitoring.

Although liquid biopsy has most often referred to the analysis of cfDNA from peripheral blood, this term also encompasses the isolation and analysis of tumor-derived material (e.g., DNA, RNA, or even intact cells) from blood or other bodily fluids. For example, intact circulating tumor cells intravasate into the bloodstream at low frequency (often <10 circulating tumor cells per milliliter of blood in patients with metastatic cancer). With specialized technology, circulating tumor cells can be detected and isolated from a background of normal blood cells, facilitating molecular analysis and even implantation and growth of these cells in immunocompromised mice. Subcellular particles called exosomes, or extracellular membrane-encased vesicles, are also released by tumor cells into the bloodstream and contain tumor-specific proteins and nucleic acids.

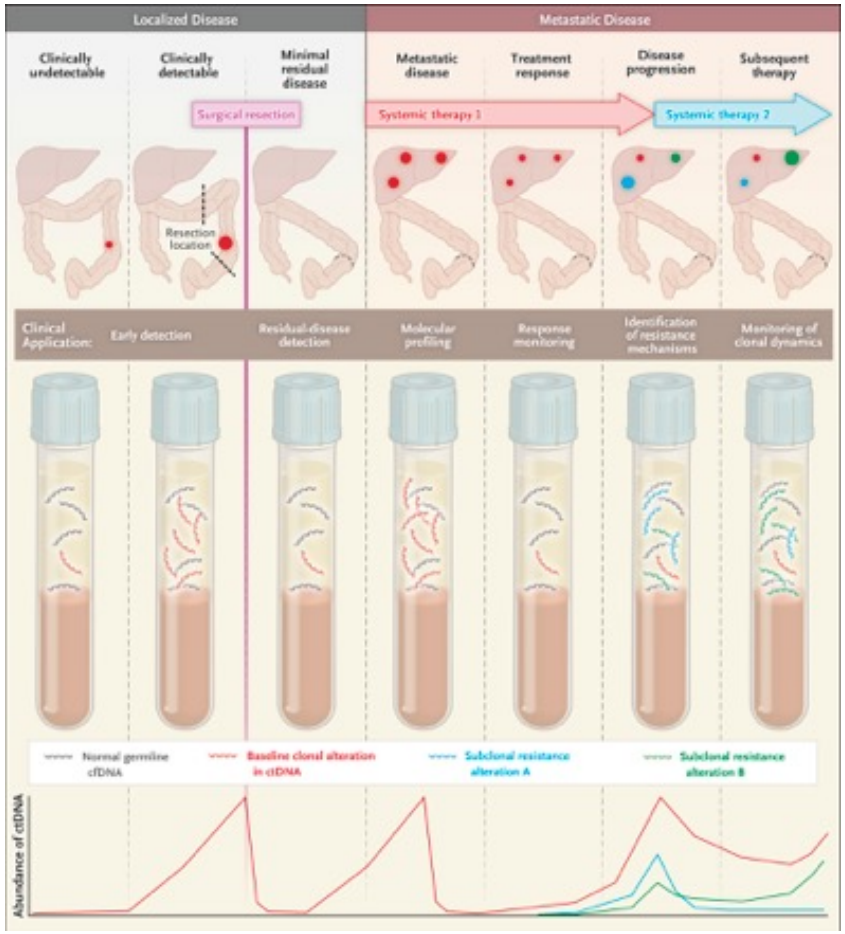


Overview of Liquid-Biopsy Approaches. Liquid-biopsy approaches involving peripheral blood include isolation of circulating tumor cells, which intravasate from tumors into the bloodstream; exosomes, which are membrane-bound vesicles released by tumor cells; and cell-free DNA (cfDNA), which is released by apoptotic or necrotic tumor cells. Although peripheral blood is the most common source of liquid biopsy, several other bodily fluids have been used for specific liquid-biopsy applications, including isolation and analysis of cfDNA, as shown.

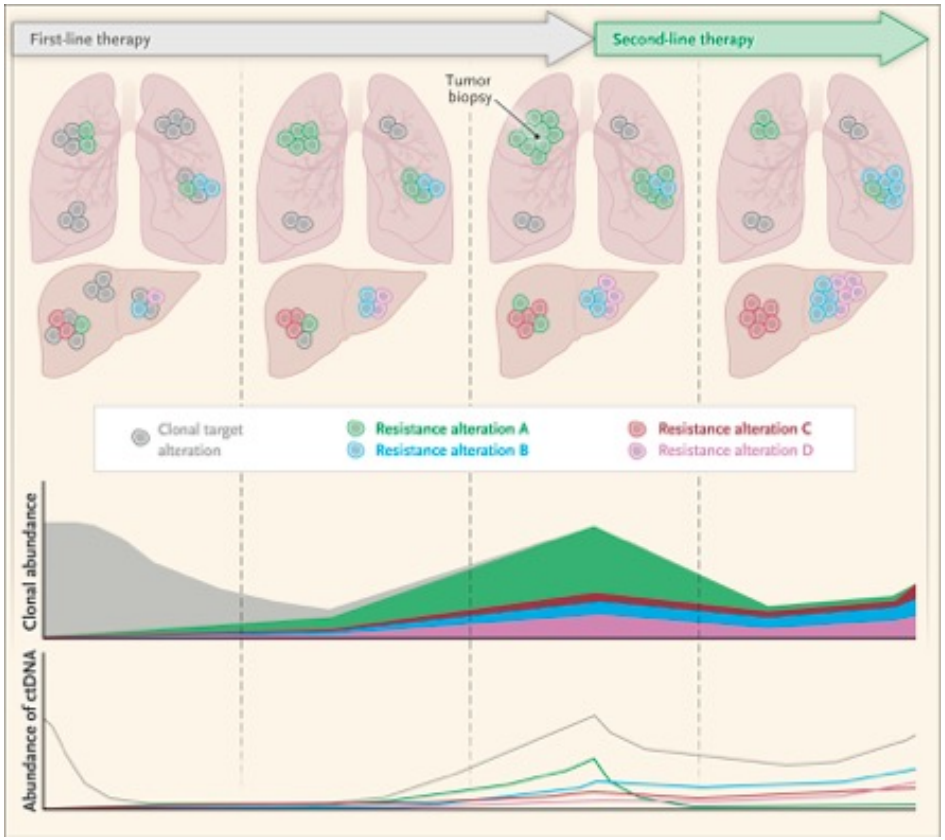
Owing to the low levels and short half-life of tumor-derived cfDNA, specialized approaches are needed for both isolation and analysis of cfDNA. Two key issues are the stability of the cfDNA itself and the potential for lysis of normal blood cells, leading to contamination with normal DNA. To limit these effects, when cfDNA is isolated from blood collected in standard phlebotomy tubes, plasma must typically be centrifuged and separated within 1 to 4 hours after collection. This need for rapid processing creates logistic challenges and the potential for preanalytic variability caused by fluctuations of cfDNA concentration and purity due to differences in processing times. Alternatively, specialized cfDNA collection tubes containing fixatives can stabilize both cfDNA and intact cells for up to 7 to 14 days at room temperature, allowing for easy shipping, storage, and batched or centralized processing. The fraction of ctDNA within the background of normal cfDNA in patients with cancer is typically small and highly variable from patient to patient. Thus, ultrasensitive methods are required to detect mutations, copy-number changes, or other alterations that are present in cfDNA at very low variant-allele frequencies (i.e., the percentage of variant alleles present among all alleles, including wild-type alleles). For detection of individual point mutations, mutation-specific techniques based on polymerase-chain-reaction (PCR) analysis — such as BEAMing (beads, emulsion, amplification, and magnetics) or droplet digital PCR (ddPCR) analysis — can identify and quantify alterations present at allele frequencies of 0.01% or less in cfDNA.



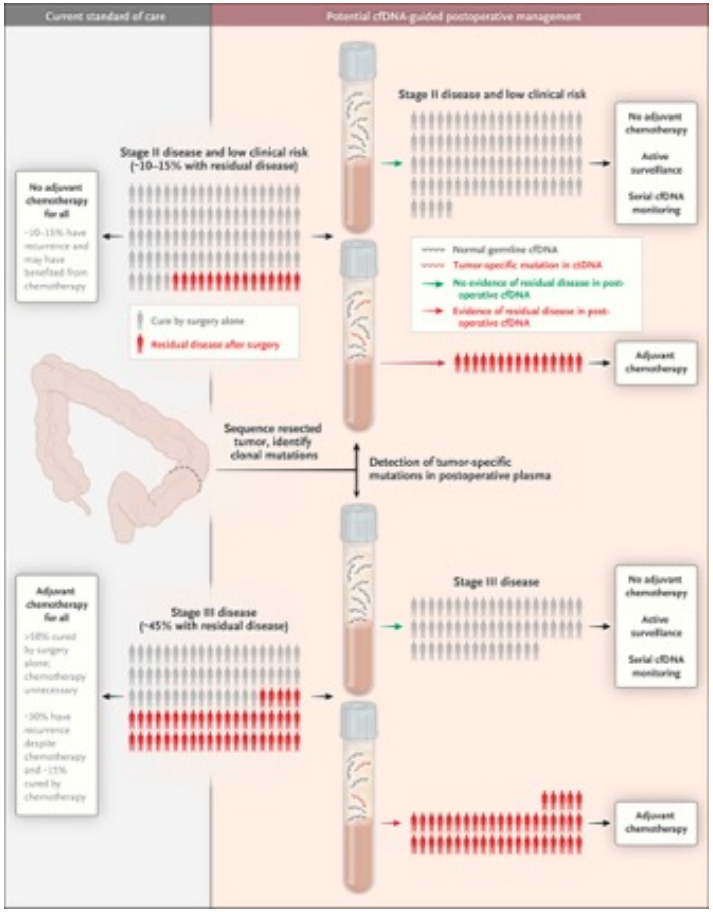
Isolation and Analysis of cfDNA. As shown on the left, cfDNA is isolated from plasma after centrifugation of peripheral blood to separate the cellular component of the blood, including white and red cells. Circulating tumor DNA (ctDNA) is found (often at low fractions) among a background of normal germline cfDNA released by normal cells throughout the body. The cfDNA can be analyzed to identify several common DNA-based alterations observed in tumors, including mutations, copy-number alterations, gene fusions, and DNA methylation changes. As shown at the upper right, owing to the frequently low fraction of ctDNA in a background of normal cfDNA, specialized methods for cfDNA analysis have been developed, including sequencing and methods based on polymerase-chain-reaction (PCR) analysis (BEAMing [beads, emulsion, amplification, and magnetics] and droplet digital PCR). Typically, those analyses providing the greatest breadth or nucleotide coverage have lesser sensitivity and require higher fractions of ctDNA in overall cfDNA (percentages in red) for analysis.



Clinical Applications of cfDNA Analysis. Analysis of cfDNA has potential applications at multiple points throughout the natural course of cancer development, diagnosis, and treatment. Early-detection methods that screen for evidence of nascent tumors in cfDNA are currently under development. A liquid-biopsy test capable of identifying early-stage cancers in asymptomatic persons may allow cancers to be identified at a stage when they are more likely to be curable. After surgery with curative intent, cfDNA from postoperative plasma drawn during the weeks after surgery can be analyzed for the persistent presence of mutations or other alterations known to exist in the patient's resected tumor. Since the half-life of cfDNA is very short (an hour or less), any evidence of persistent tumor-derived mutations in cfDNA from postoperative plasma can provide direct evidence of residual disease that may ultimately lead to tumor relapse. Detection of residual disease in cfDNA shortly after surgery may allow patients to be stratified according to risk of recurrence and may offer an opportunity for early intervention to salvage cure. In the context of metastatic disease, clinical sequencing of cfDNA can identify potentially targetable genetic alterations to select precision therapies. Sequencing of cfDNA can identify many of the same target alterations identified by tumor sequencing, which can be particularly useful when insufficient tumor material is available for clinical sequencing. Studies have suggested that ctDNA levels closely parallel overall tumor burden and can be used as an accurate means of monitoring treatment response and the development of resistance. On disease progression, cfDNA analysis has proved effective in identifying emergent genetic alterations that drive therapeutic resistance, which can guide subsequent therapy choice. Owing to the potential for extensive tumor heterogeneity in the context of acquired resistance, cfDNA analysis may identify multiple concurrent resistance alterations residing in distinct tumor metastases that would not be captured by a single tumor biopsy.



Tumor Heterogeneity and cfDNA. Acquired resistance to therapy is often thought to arise from rare tumor subclones that harbor preexisting resistance alterations. Although all cells may harbor the original clonal target alteration, preexisting subclonal alterations that provide a fitness advantage under the selective pressure of therapy may exist in some cells. As therapy is initiated, it may exert a cytotoxic effect on most tumor cells, but an outgrowth of resistant subpopulations may occur, leading to dynamic shifts in clonal abundance and eventual disease progression. Because preexisting resistant subclones may reside in different metastatic lesions or in different subpopulations within a single lesion, the emergence of resistance can be characterized by extensive molecular heterogeneity. Thus, a single tumor biopsy specimen that is obtained during disease progression may reveal only a subset (i.e., green only) of the resistant clones present, and subsequent therapies that are directed against this resistance mechanism only may lead to mixed clinical response and treatment failure due to outgrowth of other coexistent clones. Analysis of cfDNA has the potential to identify multiple concurrent mechanisms of resistance and can monitor clonal dynamics during therapy. Clonal alterations (present in the original tumor clone and thus in all cells) are represented in gray, and resistant subclonal alterations in other colors.



Use of cfDNA for the Detection of Residual Disease and Management of Postoperative Therapy. After surgery with curative intent, there is currently no way to determine which patients are cured of their disease and which have subclinical residual disease that may ultimately lead to recurrence. Thus, decisions about adjuvant chemotherapy are based on clinical-risk stratification. In the example of colon cancer, patients with stage II disease who are at low clinical risk undergo observation alone and do not receive adjuvant chemotherapy, although approximately 10 to 15% will eventually have recurrent disease. Conversely, patients with stage III disease are treated with adjuvant chemotherapy, even though more than half are cured by surgery alone. Current efforts are focused on using postoperative cfDNA to identify patients with residual disease, which may allow more precise decisions about adjuvant treatment. Briefly, tumor-specific mutations or other alterations are identified in the resected tumor specimen of each patient, and plasma specimens obtained a few weeks after surgery are assessed for the persistent presence of these alterations as direct evidence of residual tumor. With further improvement of this approach, it may be possible in future studies to assign patients who would not have received adjuvant therapy as the standard of care (i.e., with stage II disease) to receive adjuvant therapy if evidence of residual disease is detected in cfDNA. Similarly, as the sensitivity and reliability of these tests improve, it may even be possible to assign patients who would receive adjuvant therapy as the standard of care (i.e., those with stage III disease) to a low-risk group on the basis of cfDNA testing; active surveillance could be considered in lieu of adjuvant therapy, thus sparing many patients who are cured by surgery alone the toxic effects of chemotherapy.

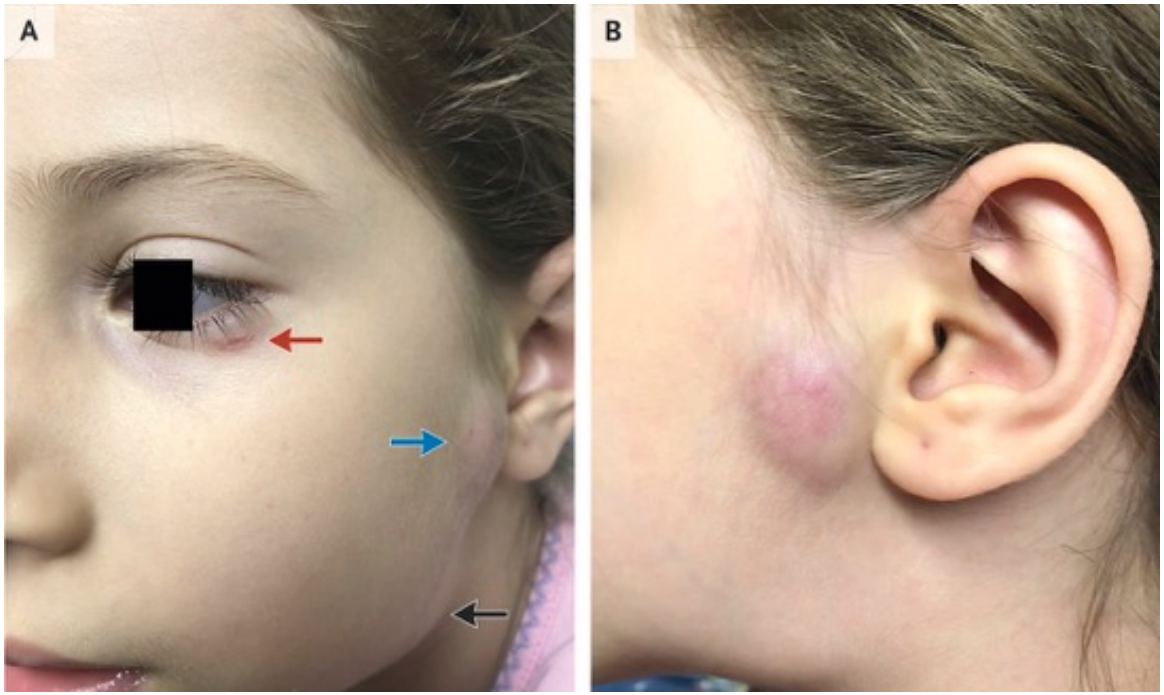
Early Cancer Detection

The holy grail of liquid-biopsy applications is the potential for early cancer detection through a simple blood test in otherwise healthy, asymptomatic persons. At present, no mature technology exists to achieve that goal, but such an approach would require a highly sensitive method — to detect trace amounts of cfDNA or other material released by precancerous lesions or early-stage cancers — and would also require high specificity to minimize false positive results in the large unaffected population undergoing screening. Additional challenges complicate this undertaking. First, since many cancer types share common mutations in genes such as *KRAS*, *BRAF*, or *TP53*, localizing a cancer to a specific organ after a positive liquid-biopsy test may be difficult.

Summary and Future Directions

Analysis of cfDNA has rapidly emerged as a technology with many promising clinical applications in oncology. Effective clinical integration of cfDNA analysis will require a careful understanding of the advantages and limitations of this approach for proper interpretation of results to guide clinical decision making. Although further prospective study is needed, cfDNA analysis harbors the potential to have a transformative effect on cancer medicine.

Parinaud's Oculoglandular Syndrome in Cat Scratch Disease

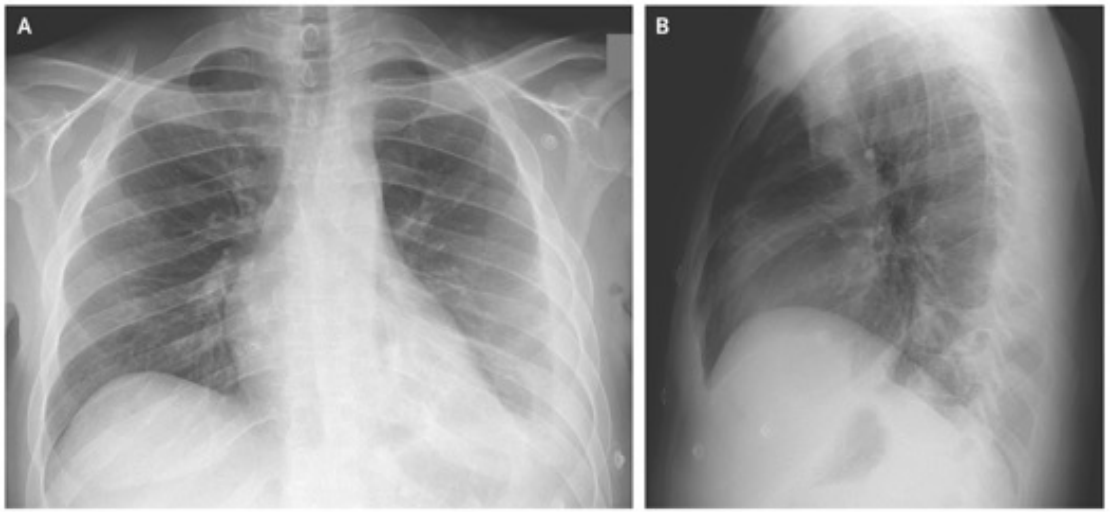


A 5-year-old girl presented to the emergency department with a preauricular mass and submandibular adenopathy on the left side of her face that had been visible for 2 months. An excoriation below the left eye (Panel A, red arrow), a fluctuant, tender preauricular mass (Panel A, blue arrow; and Panel B), and submandibular adenopathy (Panel A, black arrow) were observed on physical examination. The patient had no history of fevers, and her vision was unaffected. She frequently played with a cat at home. The preauricular mass was aspirated, and a purulent, brownish drainage was obtained. Given the high clinical suspicion of cat scratch disease, the patient was discharged with a 5-day prescription for oral azithromycin. The results of culture of the aspirate in chocolate agar were negative, but histopathological analysis of the aspirate revealed an inflammatory infiltrate with necrosis. Bacilli were detected on Warthin–Starry staining. Serologic tests were positive for the causative bacterium, *Bartonella henselae* (IgM titer, >1:1024; IgG titer, >1:20). Parinaud's oculoglandular syndrome, a manifestation of cat scratch disease, is characterized by involvement of the conjunctiva or the area around the eye, in association with preauricular lymphadenitis on the same side. The syndrome can occur when the inoculation site involves the conjunctiva or eyelid. On follow-up 2 months after treatment, the patient's preauricular and submandibular adenopathy had resolved.

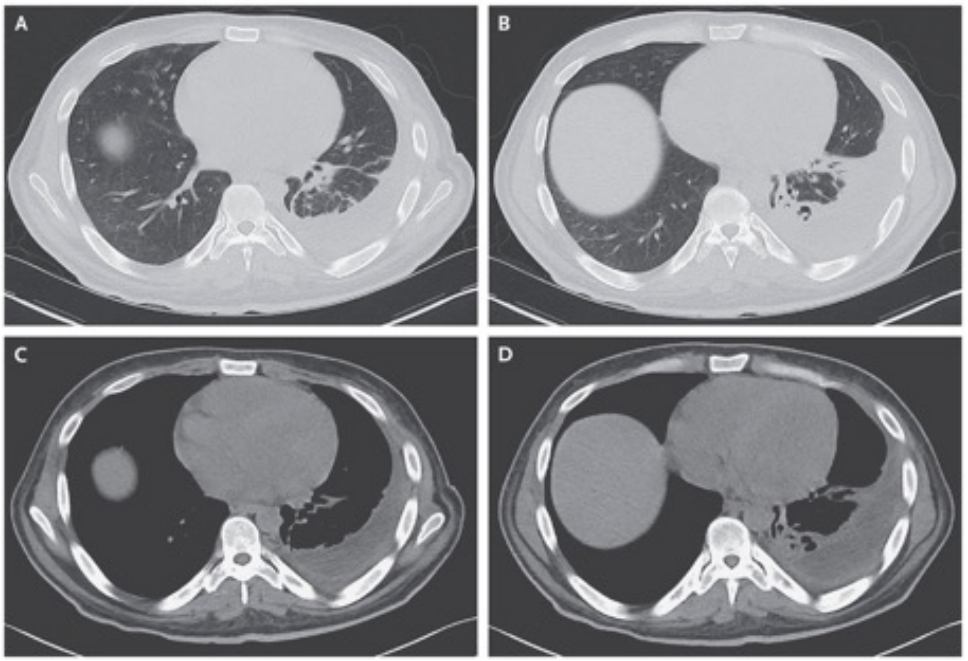
Complements from the Lung

A 26-year-old man presented to the hospital for evaluation of chest pain. Six weeks earlier, he had been admitted to another hospital for management of community-acquired pneumonia in the left lower lobe, which was complicated by hypoxemic respiratory failure that led to treatment with noninvasive positive-pressure ventilation. In the weeks after discharge, his cough and shortness of breath resolved after he completed a course of levofloxacin. Two weeks before the current presentation, chest pain developed in the patient, which steadily increased in severity. The pain was sharp, was localized to the left lower chest wall, and was exacerbated by inspiration but was unaffected by exertion or body position. In addition, the patient had chills and night sweats, but he did not note a fever. The pain was associated with nausea and episodic emesis. He reported no hemoptysis, abdominal pain, diarrhea, dysuria, polyuria, gross hematuria, swelling of the legs or feet, muscle aches, joint pains, rashes, neck pain, or headaches.

The patient's medical history was notable for type 1 diabetes mellitus. The patient had had multiple skin and soft-tissue infections, including a left axillary abscess and cellulitis 18 months before admission, a right peritonsillar abscess 9 months before admission, and a right posterior auricular abscess 6 months before admission. His medications included a mixture of regular and neutral protamine Hagedorn insulins administered twice daily. The patient also reported that he had taken naproxen for his chest pain for several days before the current presentation. He had no known drug allergies.



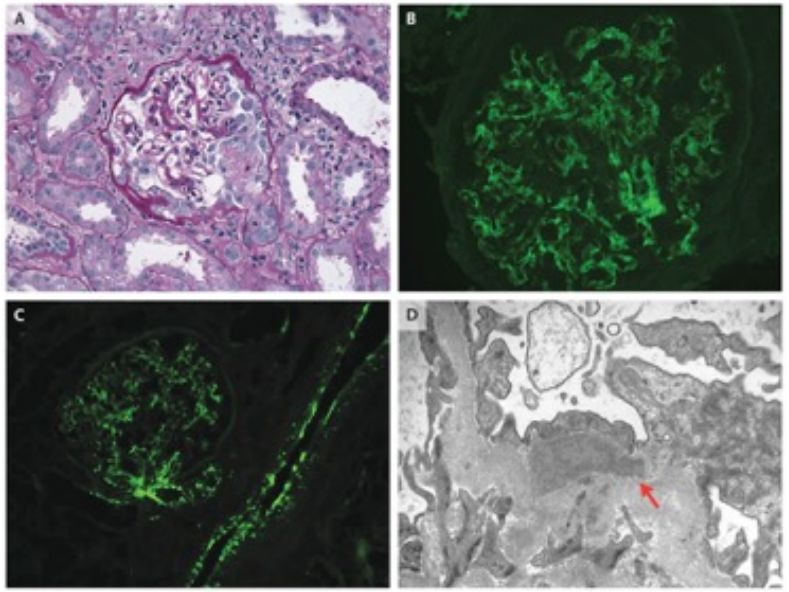
A chest radiograph obtained in the emergency department showed a left lower-lobe opacity and an adjacent pleural effusion. The serum sodium level was 130 mmol per liter, potassium 4.5 mmol per liter, chloride 90 mmol per liter, bicarbonate 23 mmol per liter, blood urea nitrogen 27 mg per deciliter (9.5 mmol per liter), creatinine 2.2 mg per deciliter (190 µmol per liter; baseline level, 0.6 to 0.7 mg per deciliter [50 to 60 µmol per liter]), and glucose 275 mg per deciliter (15.3 mmol per liter). The white-cell count was 15,100 per cubic millimeter with 86% polymorphonuclear leukocytes, 6% lymphocytes, 7% monocytes, and 0.5% eosinophils. The hemoglobin was 11.0 g per deciliter, the hematocrit was 34.7%, and the platelet count was 451,000 per cubic millimeter. Liver-function tests were normal, with the exception of a low albumin level of 2.4 g per deciliter. The lactic acid level was 1.2 mmol per liter (reference range, 0.5 to 2.2), lactate dehydrogenase (LDH) 292 U per liter (reference range, 135 to 225), and glycated hemoglobin 10.8%. Urinalysis was notable for the presence of 2+ protein and 3+ blood; microscopy revealed more than 100 red cells (of which some were dysmorphic), 20 to 50 white cells, 5 to 10 granular casts, and 0 to 2 hyaline casts per high-power field. The patient was started on vancomycin, levofloxacin, and metronidazole and was admitted to the general medical ward.



Computed Tomographic Scans of the Chest. An axial computed tomographic scan of the chest obtained at the lung-window setting shows a left lower-lobe consolidation (Panels A [upper chest view] and B [lower chest view]), and a scan obtained at the mediastinal-window setting shows an adjacent pleural effusion (Panels C [upper chest view] and D [lower chest view]).

Testing for common viral respiratory pathogens was negative. Urine antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* was negative. Diagnostic thoracentesis revealed purulent fluid that was too viscous for pH analysis, which prompted the placement of a chest tube. The glucose level, measured from the pleural fluid, was 5 mg per deciliter (0.3 mmol per liter), the amylase 8 U per liter, and the LDH higher than 2500 U per liter. Gram's staining showed 4+ polymorphonuclear leukocytes and no organisms.

By the third hospital day, the patient's creatinine level had risen to 3.2 mg per deciliter (280 μmol per liter), and a renal biopsy was performed. Light microscopy showed focal fibrinoid necrosis and an early crescentic pattern of injury; the interstitium showed focal inflammation, and few tubules contained necrotic cell debris, isolated granular casts, or red-cell casts. Electron microscopy of the glomeruli revealed moderate effacement of podocyte foot processes, as well as focal swelling and loss of fenestration in the endothelial cells. Small and ill-defined subendothelial electron-dense deposits were observed in isolated capillaries, subepithelial "hump"-like deposits were also present. Acute tubular injury with focal areas of necrosis and mild focal interstitial nephritis were also noted. A fever developed in the patient during the night after the renal biopsy; blood cultures subsequently grew methicillin-sensitive Staphylococcus aureus that was resistant to fluoroquinolones, tetracyclines, and penicillin. Because this bacterial strain was susceptible to cephalosporins, cefazolin was started and other antibiotics were discontinued.



Renal-Biopsy Specimens. Light microscopy (Panel A) shows glomerulonephritis with focal necrosis and early crescent formation. Immunofluorescence microscopy for IgA (Panel B) shows deposition in the mesangium and capillary wall. Immunofluorescence microscopy for C3 (Panel C) shows deposition in a similar distribution to IgA. Electron microscopy (Panel D) shows electron-dense deposits (red arrow).

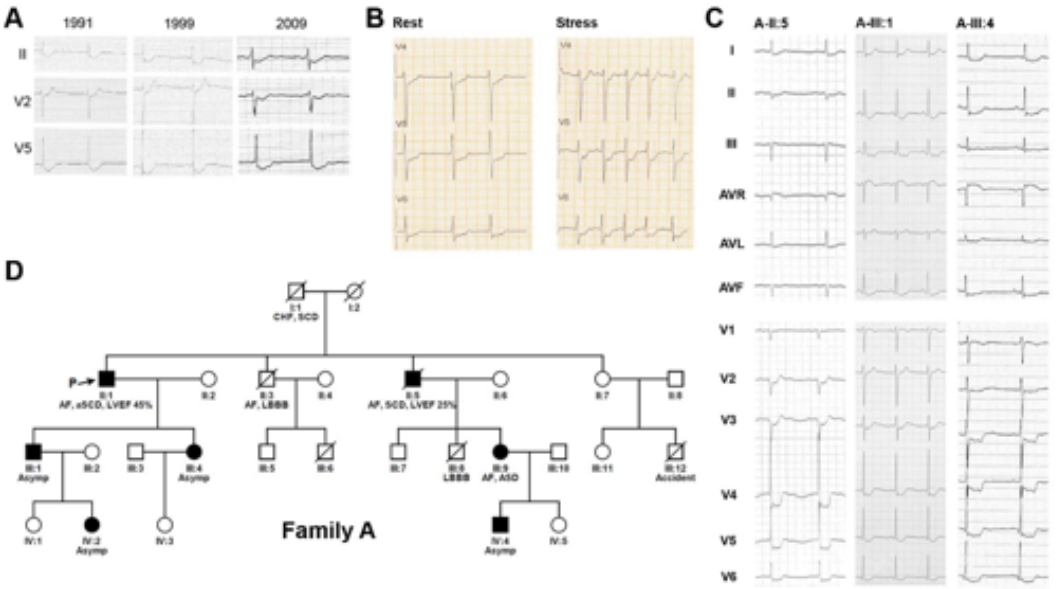
This patient presented to the hospital with pneumonia and glomerulonephritis, and additional testing quickly led to the diagnosis of empyema. Although the patient's invasive pulmonary disease was caused by bacterial infection, it was important to rule out noninfectious causes of glomerulonephritis through initial laboratory testing. Renal biopsy revealed an IgA-dominant infection-associated glomerulonephritis, which can be attributed to the patient's pleural infection and bacteremia with *S. aureus*.

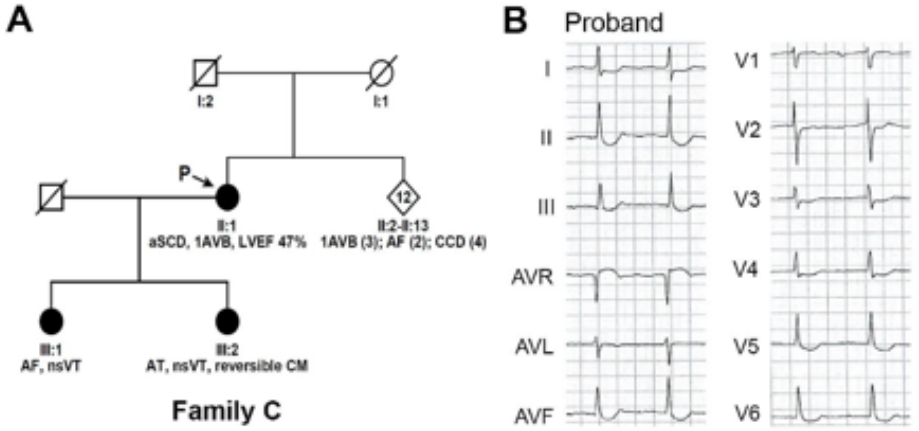
Immune-complex deposition is a hallmark of glomerulonephritis associated with infection. Renal biopsy plays an important role in making a precise diagnosis. Poststreptococcal glomerulonephritis, the prototypical type of glomerulonephritis associated with infection, is characterized by deposition of C3 and, to a lesser extent, IgG. The observation of IgA deposits on immunofluorescence microscopy (as seen in this case) led to the recognition of IgA-dominant infection-associated glomerulonephritis as a distinct condition associated with concurrent infection.[2] In addition to IgA deposits being present in IgA-dominant infection-associated glomerulonephritis, they can also be seen in glomerulonephritis caused by IgA nephropathy or IgA vasculitis (formerly Henoch–Schönlein purpura). The degree of C3 deposition can help distinguish IgA-dominant infection-associated glomerulonephritis from IgA nephropathy or IgA vasculitis because intense C3 deposition is a hallmark of IgA-dominant infection-associated glomerulonephritis.

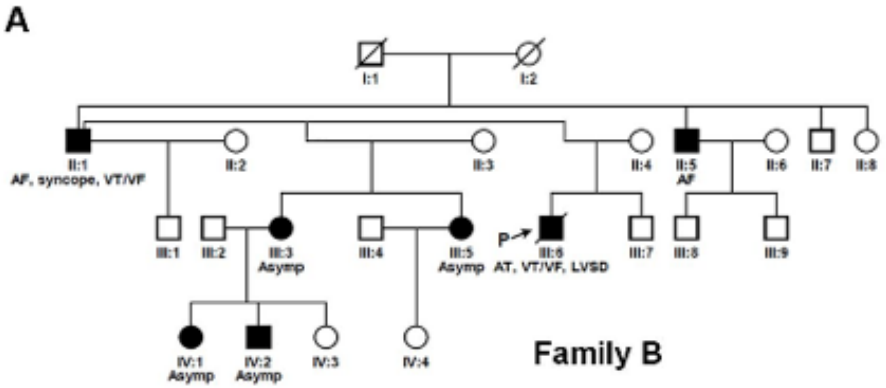
The current case of a 26-year-old man with a history of poorly controlled diabetes mellitus who presented with an invasive staphylococcal infection and glomerulonephritis is a prototypical presentation of a patient with IgA-dominant infection-associated glomerulonephritis, with the exception that the patient was of a relatively young age. The diagnosis of IgA-dominant infection-associated glomerulonephritis should be suspected in patients who present with acute glomerulonephritis in the context of infection — particularly in patients with *S. aureus* infection and in patients with diabetes.

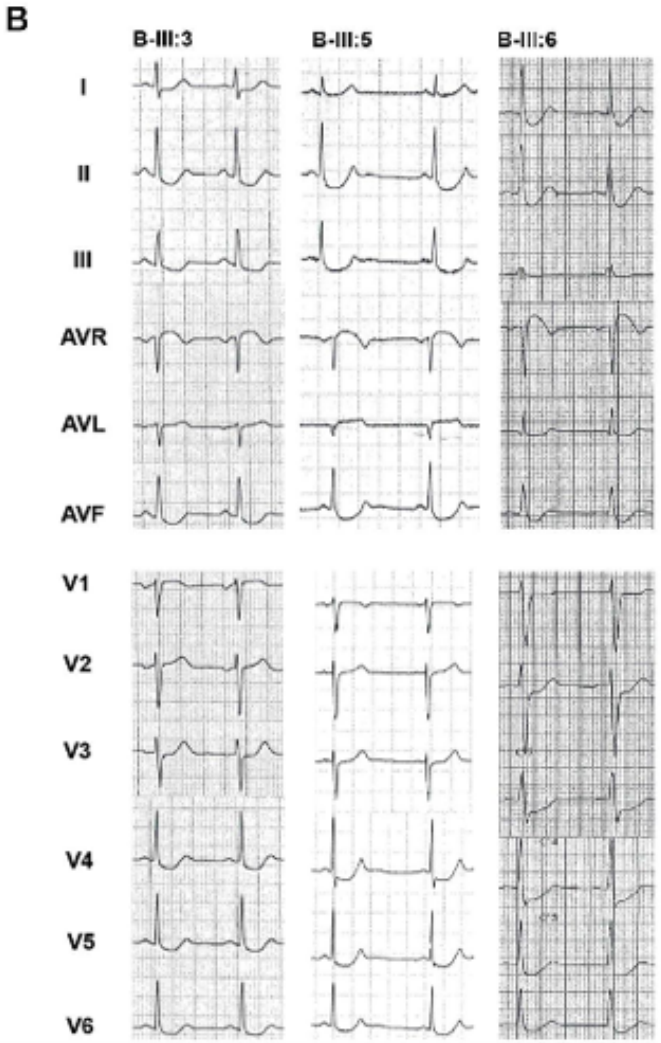
A Novel Familial Cardiac Arrhythmia Syndrome with Widespread ST-Segment Depression

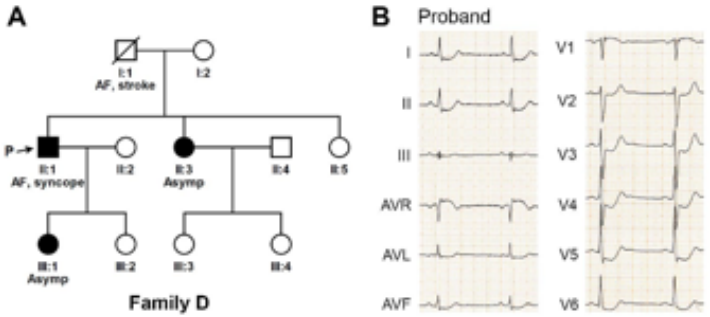
Several classic cardiac genetic disorders have been identified from specific electrocardiographic (ECG) patterns. We describe five unrelated families, from three different countries, with features that appear to represent a previously unrecognized autosomal dominant syndrome. These families were identified at three tertiary referral centers for patients with known or suspected inherited cardiac disorders. The patient remained asymptomatic until atrial fibrillation developed at 55 years of age. Eight years later, he had aborted sudden cardiac death due to ventricular fibrillation. His son and daughter had similar ECG changes, as did four additional family members. Two relatives died from sudden cardiac death. Atrial fibrillation and ventricular arrhythmias were observed in the fifth decade of life in three family members. No coronary artery disease was identified in the affected persons, and imaging showed no, or only mild, left ventricular dysfunction.

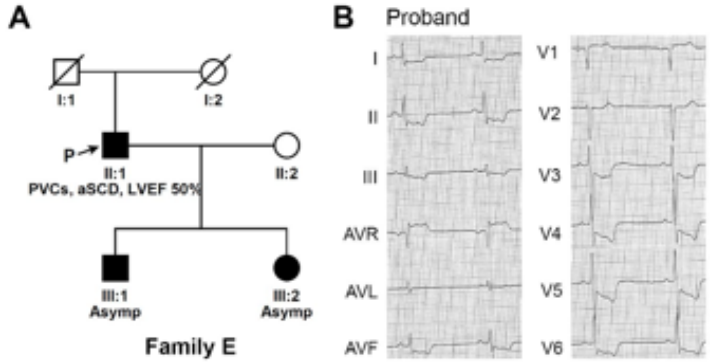










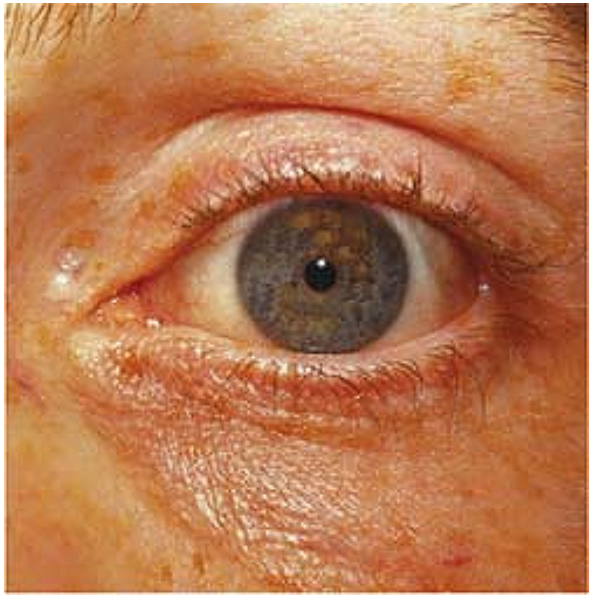


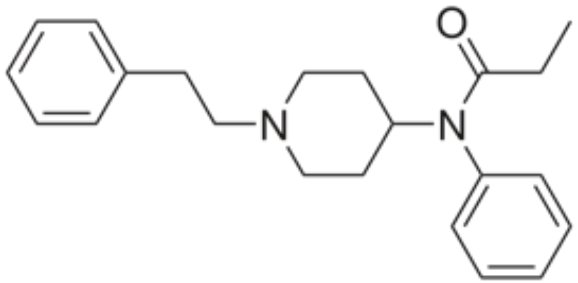
Genetic evaluations were performed at the discretion of the referring physician. Gene panels that included genes associated with cardiovascular disease were screened in all five families; all genetic tests were negative. In conclusion, we identified five families with an autosomal dominant cardiac syndrome characterized by rather uniform ECG changes with marked, persistent, nonischemic ST-segment depression, the development of atrial fibrillation and ventricular arrhythmias, and (in older persons) some degree of left ventricular dysfunction. In contrast to some other genetic disorders (e.g., the long-QT syndrome and the Brugada syndrome) that are characterized by dynamic pathognomonic ECG changes, the ST-segment depression observed here remained stable over time. On the basis of the findings in these five families, we propose diagnostic criteria for this novel syndrome

Lethal Fentanyl and Cocaine Intoxication

The opioid crisis has rapidly transitioned from prescription opioids to heroin and fentanyl. We describe an outbreak of opioid intoxication in patients who had not used opioids previously and who had nonopioid substance-use disorder. Late on a weekend evening, the first 6 patients in a clustered outbreak were brought by emergency medical services to the emergency department for suspected intoxication after they had smoked “crack” cocaine. In total, 18 patients with life-threatening poisoning presented over a period of 4 days.

The patients were found to be unresponsive with an opioid toxidrome; they had lethargy, pinpoint pupils, and respiratory depression. Most of the patients had a response to naloxone; 17 patients were administered higher doses than are normally used to reverse opioid overdose (0.4 to 6.0 mg, administered intranasally or intravenously). The median age of the patients was 53 years, and 67% were men; many were presenting to our health system for the first time. In 5 patients with prior visits who had previously undergone urine screening for drugs, all the results confirmed the presence of cocaine and an absence of other opioids, although fentanyl was not part of routine urine screens for drugs at that time. Most of the patients arrived from the same ZIP Code, which suggested a point source. A total of 3 patients died, and there were medical complications (e.g., acute kidney injury, rhabdomyolysis, and anoxic brain injury) in additional patients.



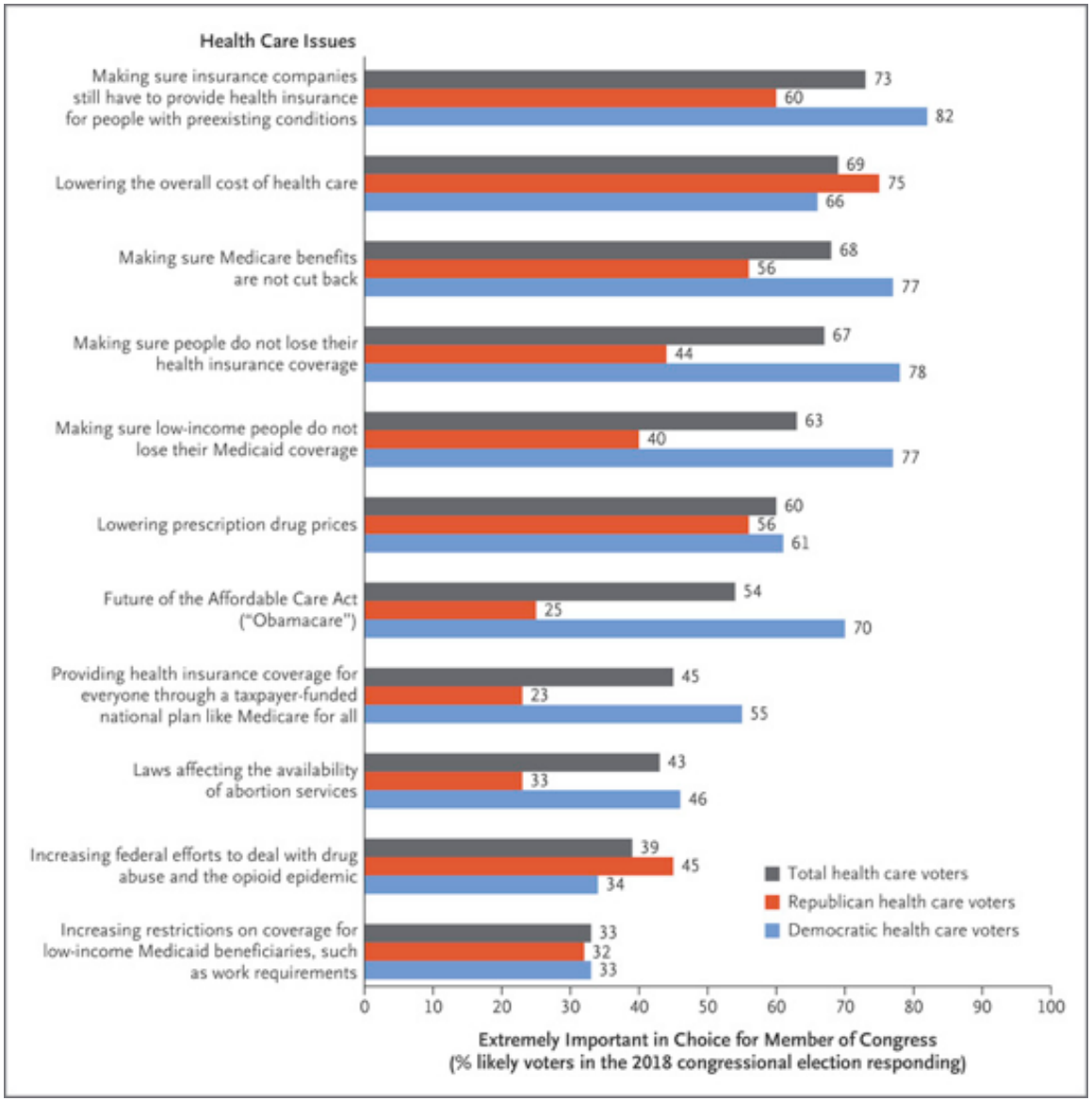


Fentanyl ist ein synthetisches Opioid, das als Schmerzmittel in der Anästhesie (bei Narkosen) sowie zur Therapie akuter und chronischer Schmerzen, die nur mit Opioidanalgetika ausreichend behandelt werden können, eingesetzt wird. Fentanyl wirkt als Agonist am μ-Opioidrezeptor. Fentanyl fällt unter das deutsche und das Betäubungsmittelgesetzt.

Health Care in the 2018 Election

The outcome of the 2018 midterm congressional election is important to the future of health care in the United States. Since 1994, the division between those who identify as Republicans and those who identify as Democrats has grown on a range of domestic policy issues, including many major health care topics. These far-reaching differences in policy preferences are increasingly reflected in the congressional voting patterns of members from both parties, particularly in the House of Representatives. Votes in Congress tend to reflect the views of party loyalists, particularly those who are activists, rather than the views held by the general populace.3 In addition, the health agenda of the next Congress will be affected not only by which party is in the majority but also by how salient specific health issues were in deciding the outcome of the midterm elections. Top-ranked issues are often given a higher priority for action by leaders of the next Congress.
the results indicate a statistical tie among the top five issues — that is, all five are within the margin of sampling error of the poll: health care, gun policy, Supreme Court nominees, the economy and jobs, and education. Every other issue on the list was seen as extremely important by at least one in five likely voters..

Rank	Total Likely Voters	Republican Likely Voters	Democratic Likely Voters
	issue (percent of respondents classifying issue as extremely important)		
1	Health care (40)	Terrorism (48)	Health care (55)
2	Gun policy (39)	Economy and jobs (47)	Education (49)
3	Supreme Court nominees (38)	Gun policy (47)	Supreme Court nominees (47)
4	Economy and jobs (37)	Immigration (43)	Environment and climate change (43)
5	Education (37)	Taxes (41)	Gun policy (43)



As shown in Figure 1, the top 4 health care issues, ranked according to the proportion of voters who said they are extremely important, are protecting health insurance coverage for those with preexisting conditions, lowering the overall cost of health care, making sure Medicare benefits are not cut back, and making sure people do not lose their health insurance coverage.

Issue	Total Voters	Republican Voters	Democratic Voters
	percent of respondents		
Role of the federal government			
Role of federal government in trying to make the health care system in the United States work better†			
Should play major role	59	37	83
Should play minor role	24	35	12
Should play no role	16	27	4
Making sure all Americans have health care coverage is ...†			
The responsibility of the federal government	54	21	88
Not the responsibility of the federal government	44	77	10
Affordable Care Act (ACA)			
View of the ACA†			
Generally favorable	51	14	87
Generally unfavorable	45	82	9
Would like to see the ACA ...‡			
Remain in place	51	10	87
Be repealed	44	85	11
Trump's alternative health plan initiative			
Expand the availability of health plans that cover fewer benefits and offer fewer protections for people with preexisting conditions than plans under the ACA, or "Obamacare." These plans are typically less expensive for younger and healthier people but may result in higher premiums for older and sicker people.†			
Favor	29	48	13
Oppose	62	39	83
Medicaid work requirement			
Require low-income, able-bodied adults without young children to work in order to receive Medicaid benefits§			
Favor	73	86	63
Oppose	23	12	34
Single payer, Medicare for all			
Replace the current health insurance system in the United States with a program in which all Americans would get their health insurance from one government insurance plan like Medicare that is financed by taxpayers†			
Favor	46	21	70
Oppose	49	76	24
Prescription drug prices			
Trump proposal to allow pharmacists to tell customers whether a direct payment would be cheaper for them than using their insurance¶			
Favor	80	88	75
Oppose	12	6	19

As shown in the Table, although 59% of likely voters overall believe that the federal government should play a major role, there are large partisan differences. Only 37% of Republican likely voters believe that the federal government should play a major role, as compared with 83% of Democratic likely voters. The second question is whether it is the responsibility of the federal government to make sure that all Americans have health insurance coverage. Once again, this question illuminates deep divisions between party loyalists: 54% of overall likely voters say that this is the responsibility of the federal government; however, only 21% of Republican likely voters believe that it is, as compared with 88% of Democratic likely voters.

Two broad public health issues are also important priorities for likely voters: abortion and gun policies. Once again, a deep division can be seen between adherents of the two parties. A majority of overall registered or likely voters believe that abortion should be legal in all or most circumstances and agree with the 1973 decision by the Supreme Court in Roe v. Wade. However, a majority of Republican likely voters disagree, favoring more restrictive abortion policies and opposing Roe v. Wade. Overall, approximately two thirds of voters believe that overturning Roe v. Wade would be a bad thing for the country, while Republicans are divided in their views.

Opioid addiction			
How serious a problem is the issue of addiction to prescription opioid pain medications for the United States?**			
Very serious	73	76	73
Somewhat serious	20	17	19
Not too serious or not at all serious	7	5	7
Abortion			
Abortion should be ...†			
Legal in all or most cases	58	31	82
Illegal in all or most cases	37	66	14
Roe v. Wade Supreme Court decision that established a woman's right to an abortion††			
Agree with decision	63	36	84
Disagree with decision	31	58	13
If *Roe v. Wade* is overturned, it would be a ...‡‡			
Good thing	23	48	5
Bad thing	66	39	90
Don't know or refused	11	13	5
Gun control			
If a candidate for Congress wants to require background checks for gun purchases at gun shows or other private sales§§			
Definitely vote for	86	85	88
Definitely vote against	9	10	9
Stricter gun laws in the United States¶¶			
Support	56	24	84
Oppose	39	70	14

Question of the Week

A 52-year-old man reports drinking approximately 30 alcohol-containing drinks per week, describes features consistent with alcohol use disorder (including use that causes problems at both home and work), and has occasional withdrawal symptoms and mildly elevated liver enzyme levels. In addition to teaching him about the harms of risky levels of alcohol consumption and informing him of treatment options such as supervised withdrawal and specialty alcohol treatment, which one of the following approaches is most likely to reduce risk of harm?

- ○ Abstinence from alcohol plus disulfiram
- ○ Abstinence from alcohol
- ○ Limiting alcohol consumption to 14 drinks per week
- ○ Abstinence from alcohol plus naltrexone
- ○ Limiting alcohol consumption to 14 drinks per week plus disulfiram

Your answer is correct.

Abstinence from alcohol plus disulfiram
Abstinence from alcohol
Limiting alcohol consumption to 14 drinks per week
Abstinence from alcohol plus naltrexone
Limiting alcohol consumption to 14 drinks per week plus disulfiram

Key Learning Point View Case Presentation ›

Patients with alcohol use disorder should be advised to abstain from alcohol, obtain specialized alcohol treatment, and start treatment with a medication such as naltrexone.

Detailed Feedback

Patients who meet criteria for alcohol use disorder first require information about the risks of excessive alcohol use. They also need specialty treatment to help them meet their goals. Given this patient's elevated liver enzyme levels and his problems at home and work, abstaining from alcohol is more likely to reduce the risk of harm than cutting back to recommended limits. The patient should be closely monitored for symptoms of alcohol withdrawal and complicated alcohol withdrawal and may need close outpatient follow-up for assessment.

Specialty treatment may include regular alcohol counseling, individual therapy, teaching of relapse prevention techniques, and participation in Alcoholics Anonymous (AA) or other mutual support meetings. A sponsor through AA can also be helpful. Formal treatment programs tend to be more intensive and require a significant commitment, but they have higher rates of positive outcomes than informal programs.

Eine Totgeburt oder Stillgeburt liegt vor, wenn nach der Geburt eines Kindes kein erkennbares Lebenszeichen nachzuweisen ist und gewisse Mindestmaße (meist 500g-1000g Körpergewicht, 25–35cm Körperlänge, 21–28 Wochen Schwangerschaftsdauer) erfüllt sind, andernfalls spricht man von Fehlgeburt. Die Mindestmaße und Lebenszeichen unterscheiden sich je nach Land, Institution und Zeitpunkt. Die Diagnose lautet Intrauteriner Fruchttod (IUFT) oder Infans mortuus. Perinatale Mortalität umfasst Totgeburten und bis eine Woche nach der Geburt gestorbene Kinder. Um Todesfälle im ersten Jahr nach der Geburt geht es bei der Säuglingssterblichkeit. Laut deutscher Personenstandsverordnung liegt (seit 1. April 1994) eine Totgeburt vor, wenn nach der Geburt eines mindestens 500 Gramm schweren Kindes kein erkennbares Lebenszeichen nachzuweisen ist, also weder das Herz geschlagen noch die Nabelschnur pulsiert oder die natürliche Lungenatmung eingesetzt hat.

Kindliche Ursachen

Ein intrauteriner Fruchttod kann auf verschiedene Ursachen zurückgeführt werden, darunter Fehlbildungen lebenswichtiger Organe, Chromosomenbesonderheiten wie Trisomie 13 oder Trisomie 18, schwerwiegende fetale Erkrankungen wie *Morbus haemolyticus fetalis*, Sauerstoffmangelversorgung durch eine unzureichende Funktion des Mutterkuchens oder dessen vorzeitige Ablösung sowie durch Nabelschnurkomplikationen, wie Nabelschnurknoten, Nabelschnurvorfall und straffe Nabelschnurumschlingung. Neue Arbeiten weisen darauf hin, dass auch ein genetisch bedingtes Long-QT-Syndrom bereits im Mutterleib zu fatalen Herzrhythmusstörungen führen könnte, was für bis zu 5 % der Totgeburten verantwortlich sein könnte.

Mütterliche Ursachen

Zu weiteren möglichen Ursachen für einen Kindstod im Mutterleib gehören Infektionen wie Listeriose, Toxoplasmose und Zytomegalie, Erkrankungen wie Eklampsie, HELLP-Syndrom und Diabetes mellitus, Drogenmissbrauch, Fehlbildungen der Gebärmutter, seltene Komplikationen wie der Gebärmutterriss und die Fruchtwasserembolie, sowie psychosozialer Stress, wie er durch Krieg, Flucht oder Vertreibung ausgelöst werden kann. Ein Kaiserschnitt bei einer vorhergehenden Schwangerschaft verdoppelt das Risiko einer Totgeburt in einer späteren Schwangerschaft.

Symptome und Diagnose

Bei Verdacht auf einen intrauterinen Fruchttod wird zunächst mithilfe des CTG versucht, eine kindliche Herzaktion nachzuweisen. Die endgültige Diagnose erfolgt jedoch durch eine Ultraschalluntersuchung, im Rahmen derer der Herzstillstand und der zum Erliegen gekommene Blutstrom in der Nabelschnur gesichert werden. Darüber hinaus zeigen sich je nach Todeszeitpunkt eine abnorme Krümmung oder Knickung der kindlichen Wirbelsäule sowie sogenannte Schädelzeichen wie die Stufenbildung der Scheitelbeine.

Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial

2·6 million pregnancies were estimated to have ended in stillbirth in 2015. The aim of the AFFIRM study was to test the hypothesis that introduction of a reduced fetal movement (RFM), care package for pregnant women and clinicians that increased women's awareness of the need for prompt reporting of RFM and that standardised management, including timely delivery, would alter the incidence of stillbirth. This stepped wedge, cluster-randomised trial was done in the UK and Ireland. Participating maternity hospitals were grouped and randomised, using a computer-generated allocation scheme, to one of nine intervention implementation dates (at 3 month intervals). This date was concealed from clusters and the trial team until 3 months before the implementation date. Treatment allocation was not concealed from participating women and caregivers. Data were derived from observational maternity data. The primary outcome was incidence of stillbirth. The primary analysis was done according to the intention-to-treat principle, with births analysed according to whether they took place during the control or intervention periods, irrespective of whether the intervention had been implemented as planned. The RFM care package did not reduce the risk of stillbirths. The benefits of a policy that promotes awareness of RFM remains unproven.

The trial intervention included an e-learning education package for all clinical staff in participating hospitals about the importance of a recent change in the frequency of fetal movements and how to manage RFM, a leaflet for pregnant women (usually distributed to women at about 20 weeks' gestation). A management plan for identification and delivery of babies at high risk was distributed to hospitals for management of women who presented with RFM from 24 weeks' gestation. The e-learning education package was created by colleagues in National Health Service (NHS) Education Scotland who had expertise in postgraduate clinician education. A link to the e-learning package was emailed to all clinicians in the participating unit about 1 month before the intended implementation of the package. The management plan for identification and delivery of babies at high risk included cardiotocography (within 2 h of presentation), measurement of liquor volume (within 12 h of presentation), and a growth scan to estimate fetal weight and abdominal circumference on the next working day (unless this latter had been done within the preceding 3 weeks).

Table 2 Stillbirth and perinatal mortality

		Intervention (n=227 860)	Control (n=157 692)	Adjusted OR (95% CI)	p value
Livebirths		226 895	156 963	..	..
Stillbirths at ≥24 weeks' gestation, n (per 1000 livebirths; primary outcome *)		921 (4·06)	691 (4·40)	0·90 (0·75–1·07)	0·232
Stillbirths, n (per 1000 livebirths; secondary outcome)					
	≥22 weeks' gestation *	933 (4·11)	704 (4·49)	0·89 (0·75–1·07)	0·213
	≥28 weeks' gestation	679 (2·99)	512 (3·26)	0·97 (0·79–1·18)	0·759
	≥37 weeks' gestation	281 (1·24)	229 (1·46)	0·94 (0·69–1·26)	0·662
	≥22 weeks' gestation in normally formed infants *	779 (3·43)	537 (3·42)	0·98 (0·80–1·21)	0·855
	≥24 weeks' gestation in normally formed infants *	771 (3·40)	528 (3·36)	0·98 (0·79–1·21)	0·825
	≥28 weeks' gestation in normally formed infants	570 (2·51)	404 (2·57)	1·02 (0·80–1·29)	0·893
	≥37 weeks' gestation in normally formed infants	239 (1·05)	189 (1·20)	0·88 (0·61–1·24)	0·457
Perinatal mortality, n (per 1000 births)		1238 (6·21)	923 (6·82)	0·98 (0·83–1·17)	0·861

Table 3 Pregnancy and baby secondary outcomes

	Intervention (n=227 860)	Control (n=157 692)	Adjusted OR (95% CI)	p value
Preterm pregnancy	17 376 (7·7%)	11 228 (7·3%)	1·05 (1·00–1·10)	0·050
Caesarean section	64 572 (28·3%)	40 231 (25·5%)	1·09 (1·06–1·12)	<0·0001
Induction at ≥39 weeks' gestation	57 815 (39·8%)	33 317 (33·6%)	1·08 (1·04–1·11)	<0·0001
Induction of labour	83 499 (40·7%)	49 952 (35·8%)	1·05 (1·02,1·08)	0·0015
Elective delivery	111 837 (54·6%)	67 227 (48·2%)	1·04 (1·01–1·07)	0·0123
Elective delivery at ≥39 weeks' gestation	76 247 (52·4%)	44 838 (45·2%)	1·05 (1·02–1·09)	0·0022
Spontaneous vaginal delivery	130 658 (57·4%)	94 337 (59·8%)	0·90 (0·88–0·92)	<0·0001
Admitted to neonatal unit	19 237 (10·1%)	13 029 (10·1%)	1·02 (0·97–1·07)	0·504
Admitted to neonatal unit for >48 h	12 676 (6·7%)	8041 (6·2%)	1·12 (1·06–1·18)	0·0001
Admitted to neonatal unit at ≥37 weeks' gestation	10 384 (6·0%)	7497 (6.5%)	0·95 (0·89–1·01)	0·091
Small for gestational age (≤10th centile) delivered ≥40 weeks' gestation	3461 (1·5%)	3081 (2·0%)	0·86 (0·78–0·95)	0·0009
Preterm baby	19 815 (8·6%)	12 738 (8·1%)	1·05 (1·00–1·10)	0·061

Added value of this study

To the best of our knowledge, this study is the first to combine RFM as an alert with an intervention designed to reduce the risk of stillbirth, and the largest study of fetal movement awareness to date. In a stepped wedge, cluster-randomised trial of 409 175 pregnancies, we showed that a package of care for pregnant women and clinicians to raise awareness of the importance of RFM, combined with a fuller assessment of fetal wellbeing and expedited delivery (where the benefits were likely to outweigh the risks), had no significant effect on the risk of stillbirth. The incidence of stillbirth at or beyond 24 weeks' gestation was 4·06 per 1000 livebirths during the intervention period and 4·40 per 1000 livebirths during the control period (adjusted odds ratio 0·90, 95% CI 0·75–1·07; p=0·232). Our secondary outcomes include a surrogate of stillbirth, the proportion of babies at or below the 10th centile of gestationally adjusted birthweight delivered at 40 weeks or more. This stillbirth surrogate was lower in the intervention group (3461 [1·5%] events of 227 860 births) than the control group (3081 [2·0%] of 157 692; p=0·001). This potential benefit has to be set against the higher frequency of caesarean section (64572 [28·4%] of 227 860 births during the intervention period *vs* 40 231 [25·5%] of 157 692 births during the control period; p<0·001] and induction rates (83 499 [40·7%] of 227 860 *vs* 49 952 [35·9%] of 157 692; p=0·001).

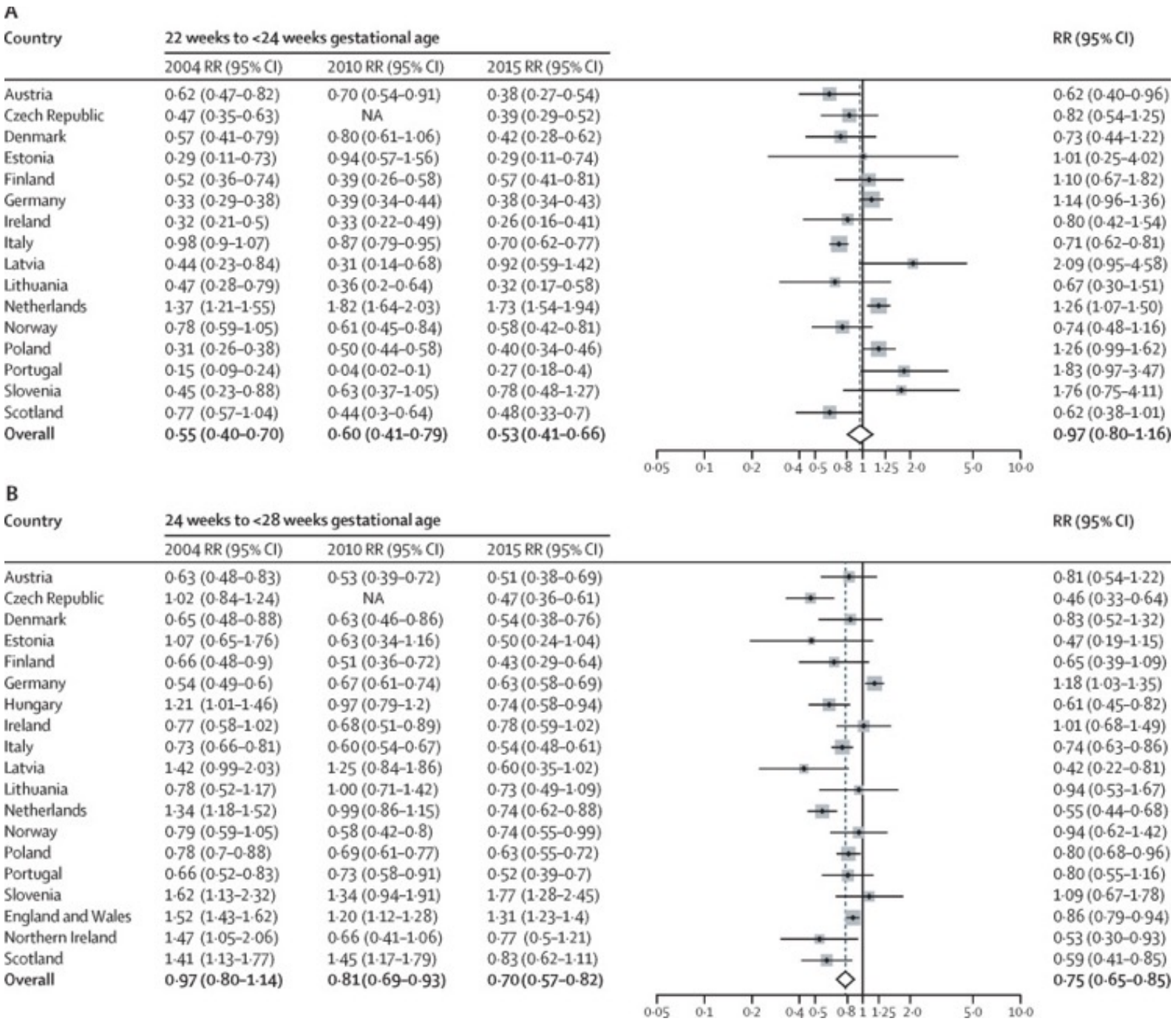
Implications of all the available evidence

RFM awareness is not supported by the research to date. Future research should include completion of other ongoing fetal movement awareness studies and a meta-analysis of data from all studies combined. An economic analysis of these data will supply additional evidence on the effectiveness of RFM awareness as a stillbirth reduction strategy, the costs, and any effects of increased rates of intervention. Such evidence will help policy makers make informed decisions about how RFM awareness might fit into a stillbirth reduction strategy.

Quantifying the burden of stillbirths before 28 weeks of completed gestational age in high-income countries: a population-based study of 19 European countries

International comparisons of stillbirth allow assessment of variations in clinical practice to reduce mortality. Currently, such comparisons include only stillbirths from 28 or more completed weeks of gestational age, which underestimates the true burden of stillbirth. With increased registration of early stillbirths in high-income countries, we assessed the reliability of including stillbirths before 28 completed weeks in such comparisons. In this population-based study, we used national cohort data from 19 European countries participating in the Euro-Peristat project on livebirths and stillbirths from 22 completed weeks of gestation in 2004, 2010, and 2015. We excluded countries without national data for stillbirths by gestational age in these periods, or where data available were not comparable between 2004 and 2015. We also excluded those countries with fewer than 10 000 births per year because the proportion of stillbirths at 22 weeks to less than 28 weeks of gestation is small. We calculated pooled stillbirth rates using a random-effects model and changes in rates between 2004 and 2015 using risk ratios (RR) by gestational age and country.

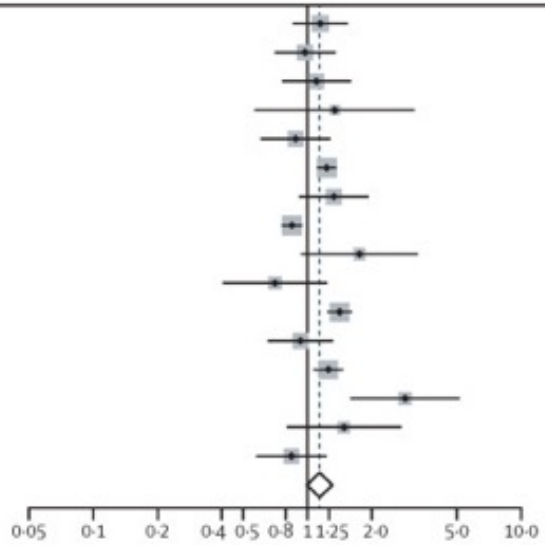
	Total births ≥22 weeks	Number of stillbirths by gestational age				Proportion of all stillbirths (%)			Inclusion of termination of pregnancy
		22 to <24 weeks	24 to <28 weeks	≥28 weeks	Unknown gestation	22 to <24 weeks	24 to <28 weeks	22 to <28 weeks	
Austria	83 884	32	43	202	0	12%	16%	27%	Excluded
Czech Republic	111 162	43	52	296	7	11%	13%	24%	Excluded
Denmark	57 847	24	31	115	0	14%	18%	32%	Excluded
Estonia	13 961	4	7	43	0	7%	13%	20%	Excluded
Finland	55 759	32	24	114	1	19%	14%	33%	Excluded
Germany	728 505	276	461	1759	63	11%	18%	29%	Excluded
Hungary	92 206	120	68	338	0	23%	13%	36%	Excluded
Ireland	65 913	17	51	222	0	6%	18%	23%	Excluded
Italy	486 557	338	261	1175	6	19%	15%	34%	Excluded
Latvia	21 826	20	13	73	0	19%	12%	31%	Included 22 to <24 weeks *
Lithuania	31 601	10	23	90	3	8%	18%	26%	Excluded
Netherlands	169 234	292	124	358	35	36%	15%	51%	Included ≥22 but rare ≥24 weeks †
Norway	59 928	35	44	134	1	16%	21%	37%	Excluded
Poland	376 968	149	237	932	3	11%	18%	29%	Excluded



Rates of stillbirth per 1000 total births by country in 2004, 2010, and 2015 and risk ratio for 2015 versus 2004 by country 22 weeks to less than 24 weeks (A) and 24 weeks to less than 28 weeks of gestation (B). NA=not applicable.

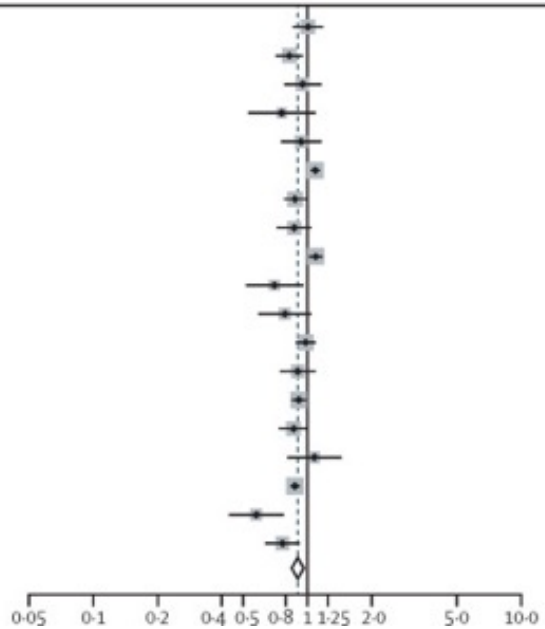
A

Country	22 weeks to <24 weeks gestational age (total births)			RR (95% CI)
	2004	2010	2015	
Austria	79	109	96	1·15 (0·85–1·55)
Czech Republic	68	NA	75	0·97 (0·70–1·35)
Denmark	56	81	55	1·10 (0·76–1·60)
Estonia	9	26	12	1·34 (0·57–3·18)
Finland	60	44	51	0·88 (0·61–1·28)
Germany	636	710	847	1·23 (1·11–1·37)
Ireland	47	52	66	1·33 (0·91–1·93)
Italy	716	690	543	0·84 (0·76–0·94)
Latvia	15	9	28	1·75 (0·94–3·28)
Lithuania	28	27	21	0·70 (0·40–1·24)
Netherlands	376	514	494	1·41 (1·24–1·62)
Norway	63	60	61	0·93 (0·65–1·32)
Poland	264	434	348	1·25 (1·07–1·47)
Portugal	16	19	36	2·87 (1·59–5·17)
Slovenia	16	34	27	1·48 (0·80–2·75)
Scotland	57	50	49	0·84 (0·57–1·23)
Overall				**1·14 (0·99–1·31)**



B

Country	24 weeks to <28 weeks gestational age (total births)			RR (95% CI)
	2004	2010	2015	
Austria	275	341	292	1·00 (0·85–1·18)
Czech Republic	384	NA	357	0·82 (0·71–0·95)
Denmark	208	206	176	0·95 (0·78–1·16)
Estonia	68	65	51	0·76 (0·53–1·09)
Finland	171	154	154	0·93 (0·75–1·16)
Germany	2823	2912	3314	1·09 (1·03–1·14)
Hungary	588	501	494	0·87 (0·78–0·98)
Ireland	230	268	210	0·87 (0·72–1·04)
Italy	1589	1816	1560	1·09 (1·02–1·17)
Latvia	94	75	70	0·70 (0·51–0·95)
Lithuania	103	101	86	0·78 (0·59–1·04)
Netherlands	702	674	638	0·98 (0·88–1·09)
Norway	213	176	200	0·90 (0·74–1·09)
Poland	1390	1431	1329	0·91 (0·84–0·98)
Portugal	377	307	254	0·86 (0·73–1·01)
Slovenia	81	100	99	1·08 (0·80–1·44)
England and Wales	3419	3196	3209	0·87 (0·83–0·92)
Northern Ireland	115	97	72	0·57 (0·43–0·77)
Scotland	258	260	201	0·76 (0·63–0·92)
Overall				**0·90 (0·84–0·96)**



Total births in 2004, 2010, and 2015 and rate ratio of gestation specific birth rate in 2015 compared with 2004 by country 22 weeks to less than 24 weeks (A) and 24 weeks to less than 28 weeks of gestation (B). NA=not applicable.

Added value of this study

We used data from 19 countries participating in the international Euro-Peristat project that collected data for births and deaths starting at 22 completed weeks of gestation in 2004, 2010, and 2015. This project had a standardised protocol with consistent international reporting practices for terminations of pregnancy and agreed definitions for reporting of stillbirths and livebirths. We estimated 32% of stillbirths were not identified using the gestational age cutoff of 28 weeks, which is recommended for international studies. The pooled stillbirth rate at 24 weeks to less than 28 weeks declined from 0·97 to 0·70 per 1000 births from 2004 to 2015, a reduction of 25% (risk ratio [RR] 0·75, 95% CI 0·65–0·85) in line with that reported in international studies on stillbirths over 28 weeks of gestation. The pooled stillbirth rate at 22 weeks to less than 24 weeks of gestation in 2015 was 0·53 and did not significantly change over time (RR 0·97, 95% CI 0·80 −1·16) but trends varied widely between countries (RRs 0·62–2·09) with evidence of differing ascertainment between countries at these earlier gestations.

Implications of all the available evidence

Current definitions used for international comparisons exclude a third of stillbirths. International consistency of reporting stillbirths at 24 weeks to less than 28 weeks suggests that to ensure that the magnitude of the burden of stillbirth is better understood and to improve routine data for monitoring of the outcomes and management of extremely preterm births, WHO's threshold for international comparisons should be lowered, at least for high-income countries. This would have a major impact, acknowledging the burden of perinatal death to families and making international assessments more informative for clinical practice and policy. Ascertainment of fetal deaths at 22 weeks to less than 24 weeks should be stabilised so that all stillbirths from 22 completed weeks of gestation onwards can be reliably compared. Contrary to speculation, stillbirths at 24 weeks to less than 28 weeks are declining in a similar manner to stillbirths seen at later gestations in European and other high-income countries. Stillbirths occurring from 22 weeks to less than 24 weeks of gestation have remained steady over time, but this is likely to be related to improvements in the reporting of deaths at these gestations. Improvements in the ascertainment of stillbirths at 22 weeks and 23 weeks of gestation within countries will allow the routine reporting of all stillbirths from 22 completed weeks of gestation onwards or even earlier internationally. This would lead to better alignment of the gestational age at which stillbirths and neonatal deaths are reported.

Stillbirths count, but it is now time to count them all

In 2015, 2·6 million stillbirths were estimated globally, more than 7100 deaths a day, with most occurring in developing countries.[1]
These figures are substantial, yet they are an underestimation of the full extent of this loss because stillbirths at less than 28 weeks of pregnancy are not included in these numbers.[2]
If the 22-week threshold was applied, the numbers have been estimated to be 40% higher.[2]
Survival of very preterm babies has increased considerably over the past decades in high-income countries (HICs),[3]
and the threshold of viability at birth has been reviewed over time.
Although WHO recommends the 28-week threshold for international comparison of stillbirths, WHO and the International Statistical Classification of Diseases and Related Health Problems 10th Revision both recommend 22 weeks of gestation as a threshold for ascertainment of fetal death, with registration and collation of data from 22 weeks. However, international differences in legislation, especially in HICs with differing policies on viability at extremes of gestational age and other factors including fatalism and a lack of accountability, lead to under-reporting of stillbirths. In *The Lancet*, Lucy K Smith and colleagues
quantified the burden of stillbirths before 28 weeks in Europe. In this population-based study, they used national cohort data from 19 European countries, collected between 2004 and 2015, with pregnancy outcomes from 22 weeks, and calculated pooled stillbirth rates and changes in rates. In 2015, more than 9000 babies were stillborn from just over 2·5 million births in Europe, and of these 6294 (32%) were stillbirths between 22 weeks and 28 weeks of gestation. The pooled stillbirth rate at 24 weeks to less than 28 weeks declined from 0·97 per 1000 births (95% CI 0·80–1·14) to 0·70 per 1000 births (0·57–0·82) between 2004 and 2015, a reduction of 25% (risk ratio [RR] 0·75, 95% CI 0·65–0·85). The pooled stillbirth rate between 22 weeks and less than 24 weeks in 2015 was 0·53 per 1000 births with no significant changes over time (RR 0·97, 95% CI 0·80–1·16), although changes did vary between countries (RRs 0·62–2·09).

Changes in health in the countries of the UK and 150 English Local Authority areas 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

Previous studies have reported national and regional Global Burden of Disease (GBD) estimates for the UK. Because of substantial variation in health within the UK, action to improve it requires comparable estimates of disease burden and risks at country and local levels. The slowdown in the rate of improvement in life expectancy requires further investigation. We use GBD 2016 data on mortality, causes of death, and disability to analyse the burden of disease in the countries of the UK and within local authorities in England by deprivation quintile. We extracted data from the GBD 2016 to estimate years of life lost (YLLs), years lived with disability (YLDs), disability-adjusted life-years (DALYs), and attributable risks from 1990 to 2016 for England, Scotland, Wales, Northern Ireland, the UK, and 150 English Upper-Tier Local Authorities. We estimated the burden of disease by cause of death, condition, year, and sex. We analysed the association between burden of disease and socioeconomic deprivation using the Index of Multiple Deprivation. We present results for all 264 GBD causes of death combined and the leading 20 specific causes, and all 84 GBD risks or risk clusters combined and 17 specific risks or risk clusters.

		UK	England	Scotland	Wales	Northern Ireland
Both YLLs	All causes	9222	8941	11195	10080	10090
	Ischaemic heart disease	1099	1040	1457	1318	1344
	Trachea, bronchus, and lung cancer	649	623	856	701	699
	Cerebrovascular disease	452	431	630	485	501
	Chronic obstructive pulmonary disease	419	408	512	437	425
	Alzheimer's disease and other dementias	352	346	378	402	378
	Self-harm	349	326	507	410	495
	Lower respiratory infections	337	336	337	322	390
	Cirrhosis and other chronic liver diseases	318	302	460	349	294
	Colon and rectum cancer	295	286	338	337	338
	Breast cancer	276	271	303	302	288
Female YLLs	All causes	7365	7164	8839	7905	7750
	Ischaemic heart disease	610	570	862	747	773
	Trachea, bronchus, and lung cancer	541	516	757	571	543
	Breast cancer	526	517	572	576	548
	Cerebrovascular disease	401	380	567	433	
	Alzheimer's disease and other dementias	368	361	393	415	390
	Chronic obstructive pulmonary disease	364	350	472	384	375
	Lower respiratory infections	283	282	279	278	328
	Colon and rectum cancer	234	227	275	255	263
	Congenital birth defects	224	221	216	233	312
	Cirrhosis and other chronic liver diseases	223	212	328	244	205
Male YLLs	All causes	11236	10864	13805	12423	12651
	Ischaemic heart disease	1637	1557	2129	1949	1986
	Trachea, bronchus, and lung cancer	772	743	976	847	878
	Self-harm	546	509	767	670	836
	Cerebrovascular disease	511	488	702	546	561
	Chronic obstructive pulmonary disease	489	479	570	506	495
	Cirrhosis and other chronic liver diseases	415	395	601	459	387
	Lower respiratory infections	404	402	411	377	472
	Colon and rectum cancer	363	352	410	428	422
	Alzheimer's disease and other dementias	323	317	352	379	355
	Prostate cancer	308	307	309	327	311
Both YLDs	All causes	11035	11054	11054	10820	10827
	Low back and neck pain	1795	1820	1654	1692	1645
	Skin and subcutaneous diseases	1036	1043	1003	989	977
	Migraine	732	719	809	785	786
	Depressive disorders	668	664	702	673	686
	Sense organ diseases	651	667	570	559	593
	Anxiety disorders	442	435	464	451	567
	Falls	364	364	374	357	361
	Oral disorders	354	355	353	347	347
	Asthma	354	348	397	368	371
	Other musculoskeletal disorders	322	323	317	317	295
Female YLDs	All causes	11741	11773	11667	11451	11546
	Low back and neck pain	2023	2056	1841	1885	1847
	Skin and subcutaneous diseases	1149	1158	1112	1095	1082
	Migraine	965	946	1086	1045	1043
	Depressive disorders	791	784	850	796	822
	Sense organ diseases	627	641	556	546	574
	Anxiety disorders	567	557	595	582	729
	Other musculoskeletal disorders	375	375	379	377	360
	Asthma	374	367	430	392	403
	Oral disorders	366	367	366	360	360
	Falls	325	326	333	315	308

The all-cause age-standardised YLL rate in 2016 was highest in Scotland (11 195 [10 177–12 389] per 100 000 population) and lowest in England (8941 [8847–9028]), with ischaemic heart disease, lung cancer, cerebrovascular disease, and chronic obstructive pulmonary disease highest in Scotland (figure 1). Age-standardised YLDs were highest in England (11 054 [8211–14 261]) and Scotland (11 054 [8188–14 304]) and lowest in Wales (10 820 [8030–14 039]); however, the range of YLDs across the UK countries only varied by 234 per 100 000 population per year compared with a range of 2254 per 100 000 population per year for YLLs. England had the highest YLD rates for low back and neck pain, skin conditions and sense organ disease, and anxiety was highest in Northern Ireland.

The ten leading risk factors contributing to YLLs were similar in rank across the four countries of the UK (figure 2). Although the ranks were similar, the PAF of each risk factor varied in size in different countries, such as a higher PAF from tobacco in Scotland, and from alcohol and drug use in Scotland and Northern Ireland, compared with the other UK nations.

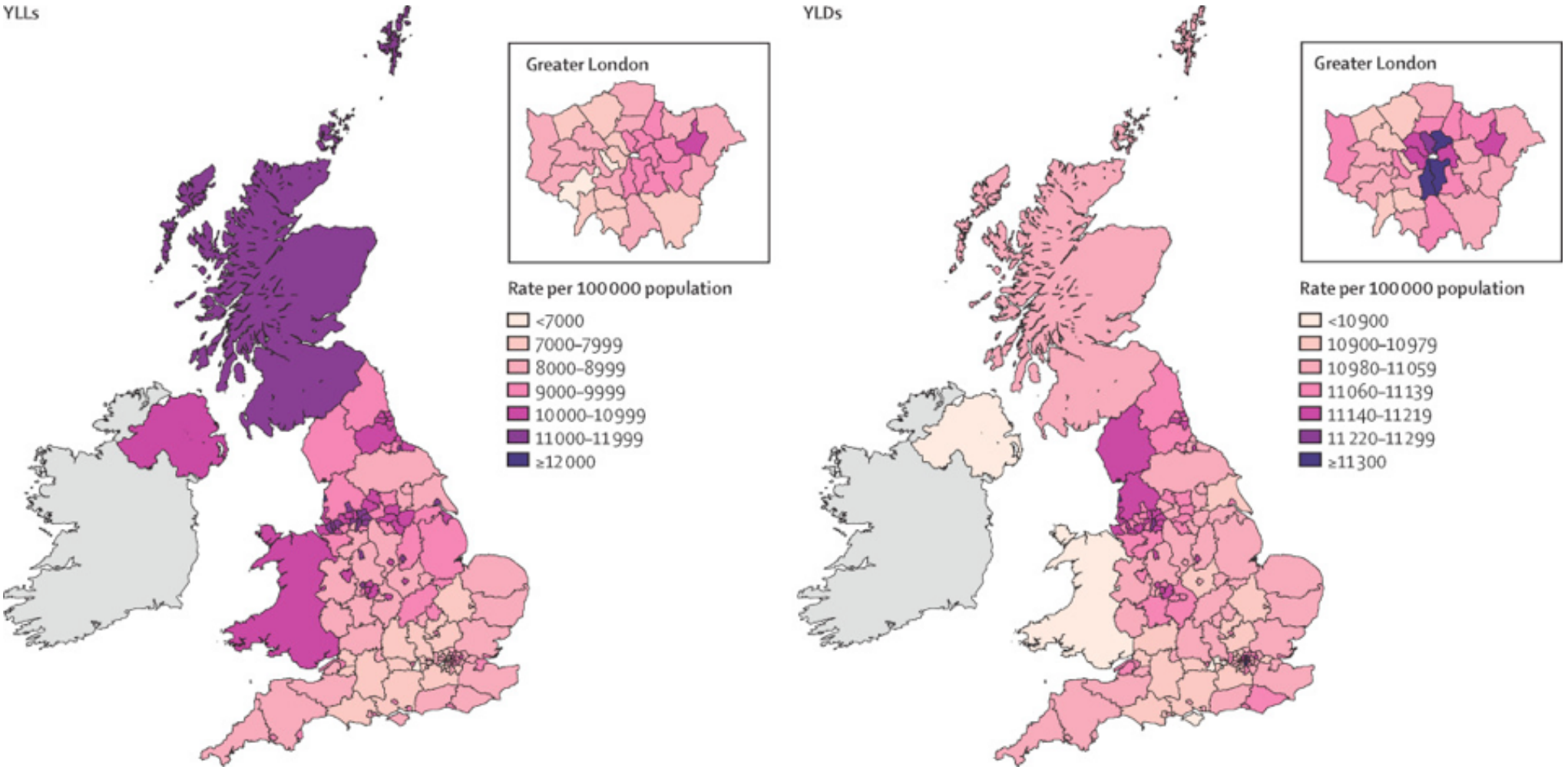
		UK	England	Scotland	Wales	Northern Ireland
Male YLDs	All causes	10324	10331	10421	10188	10093
	Low back and neck pain	1557	1576	1454	1491	1432
	Skin and subcutaneous diseases	923	930	893	884	870
	Sense organ diseases	678	695	587	574	615
	Depressive disorders	543	543	548	548	546
	Migraine	496	491	521	523	522
	Falls	400	399	411	397	413
	Drug use disorders	371	362	472	423	249
	Oral disorders	341	342	339	334	333
	Asthma	333	330	363	344	338
	Anxiety disorders	317	313	330	319	402
Both DALYs	All causes	20257	19995	22249	20900	20917
	Low back and neck pain	1795	1820	1654	1692	1645
	Ischaemic heart disease	1200	1139	1567	1428	1471
	Skin and subcutaneous diseases	1060	1068	1028	1012	999
	Migraine	732	719	809	785	786
	Depressive disorders	668	664	702	673	686
	Trachea, bronchus, and lung cancer	660	633	870	712	711
	Sense organ diseases	651	667	570	559	593
	Cerebrovascular disease	598	570	825	650	657
	Chronic obstructive pulmonary diseases	519	507	618	533	521
	Drug use disorders	465	443	714	531	304
Female DALYs	All causes	19106	18937	20506	19356	19296
	Low back and neck pain	2023	2056	1841	1885	1847
	Skin and subcutaneous diseases	1174	1184	1136	1118	1104
	Migraine	965	946	1086	1045	1043
	Depressive disorders	791	784	850	796	822
	Ischaemic heart disease	688	647	945	829	869
	Sense organ diseases	627	641	556	546	574
	Anxiety disorders	567	557	595	582	729
	Breast cancer	566	556	618	624	595
	Trachea, bronchus, and lung cancer	550	525	769	580	552
	Cerebrovascular disease	544	517	755	587	600
Male DALYs	All causes	21559	21195	24226	22611	22744
	Ischaemic heart disease	1763	1680	2268	2089	2147
	Low back and neck pain	1557	1576	1454	1491	1432
	Skin and subcutaneous diseases	946	953	917	907	892
	Trachea, bronchus, and lung cancer	785	755	992	860	892
	Sense organ diseases	678	695	587	574	615
	Cerebrovascular disease	661	631	909	724	724
	Drug use disorders	658	617	1118	789	389
	Chronic obstructive pulmonary disease	605	595	692	617	608
	Self-harm	554	517	775	678	844
	Depressive disorders	543	543	548	548	546

Significantly lower than UK mean Significantly higher than UK mean

Many conditions were important contributors to burden for both sexes, but there were differences. For YLLs, men had higher rates for all ten leading conditions than did women, except for dementia and breast cancer. Ischaemic heart disease was the leading cause of YLLs in both sexes, yet the rate was about 2·5 times higher in men than it was in women. Self-harm was the third highest YLL for men (546 [422–596]), but was fourteenth highest for women (153 [146–162]). Prostate cancer and breast cancer were important causes of premature mortality for both sexes, but breast cancer YLLs ranked higher for women than prostate cancer did for men. For YLDs, women had higher rates of disability for all the ten leading conditions than did men, except for sense organ diseases, falls, and drug use disorders.

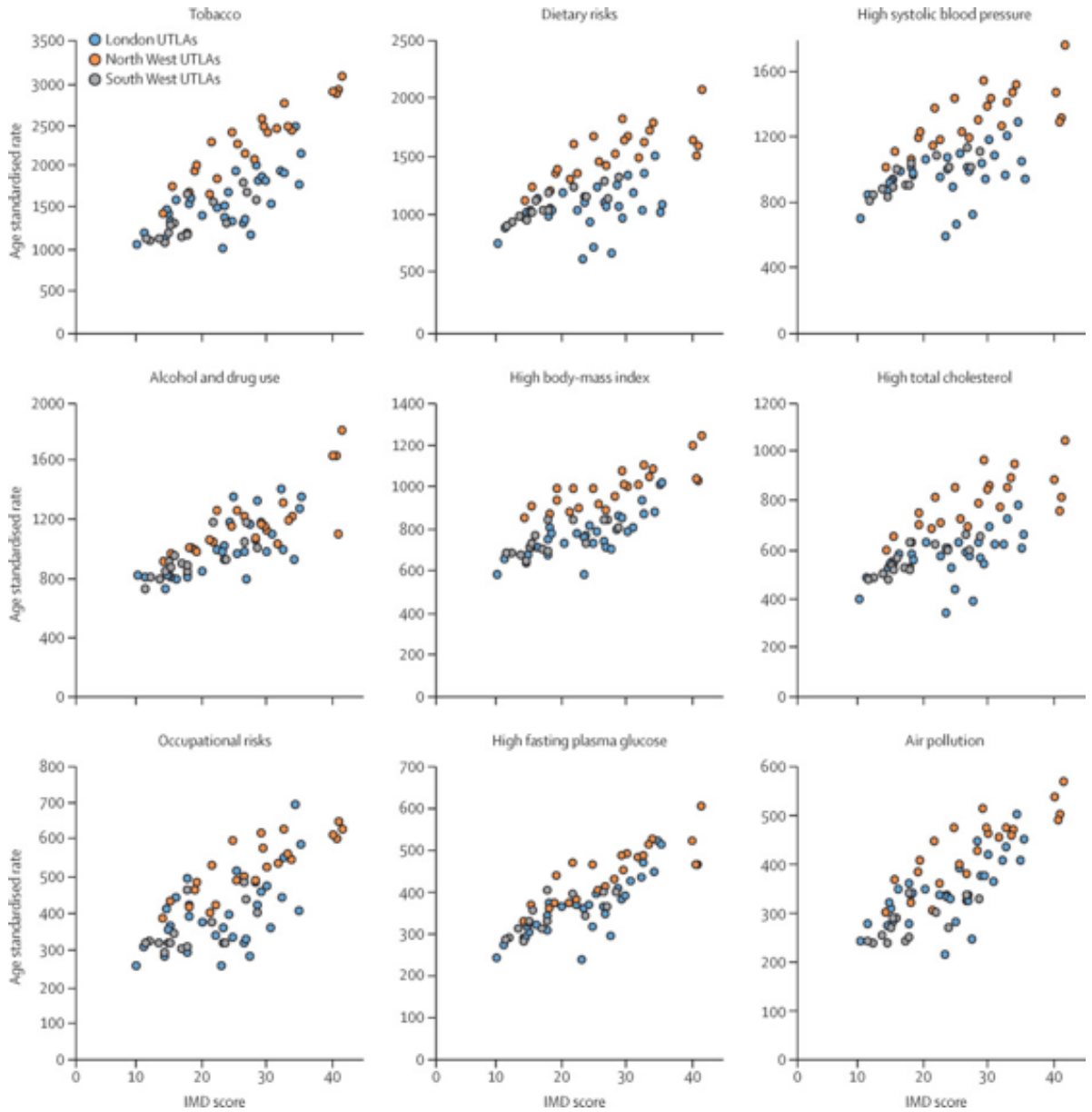
Rank	England	PAF (%)	Scotland	PAF (%)	Wales	PAF (%)	Northern Ireland	PAF (%)
1	Tobacco	19·26	Tobacco	22·76	Tobacco	20·31	Tobacco	20·01
2	Dietary risks	14·41	Dietary risks	16·12	Dietary risks	16·35	Dietary risks	15·88
3	High blood pressure	13·04	High blood pressure	14·62	High blood pressure	15·53	High blood pressure	14·99
4	High body-mass index	9·57	Alcohol and drug use	12·98	High body-mass index	9·85	Alcohol and drug use	11·50
5	Alcohol and drug use	9·52	High body-mass index	10·70	Alcohol and drug use	9·59	High body-mass index	9·97
6	High total cholesterol	7·44	High total cholesterol	8·49	High total cholesterol	8·07	High total cholesterol	8·35
7	Occupational risks	4·85	High fasting plasma glucose	5·02	High fasting plasma glucose	5·20	High fasting plasma glucose	5·18
8	High fasting plasma glucose	4·84	Occupational risks	4·63	Occupational risks	4·55	Occupational risks	4·30
9	Air pollution	4·04	Air pollution	3·87	Air pollution	3·91	Air pollution	3·58
10	Low physical activity	2·16	Impaired kidney function	2·48	Low physical activity	2·03	Low physical activity	2·52

Behavioural
Environmental and occupational
Metabolic



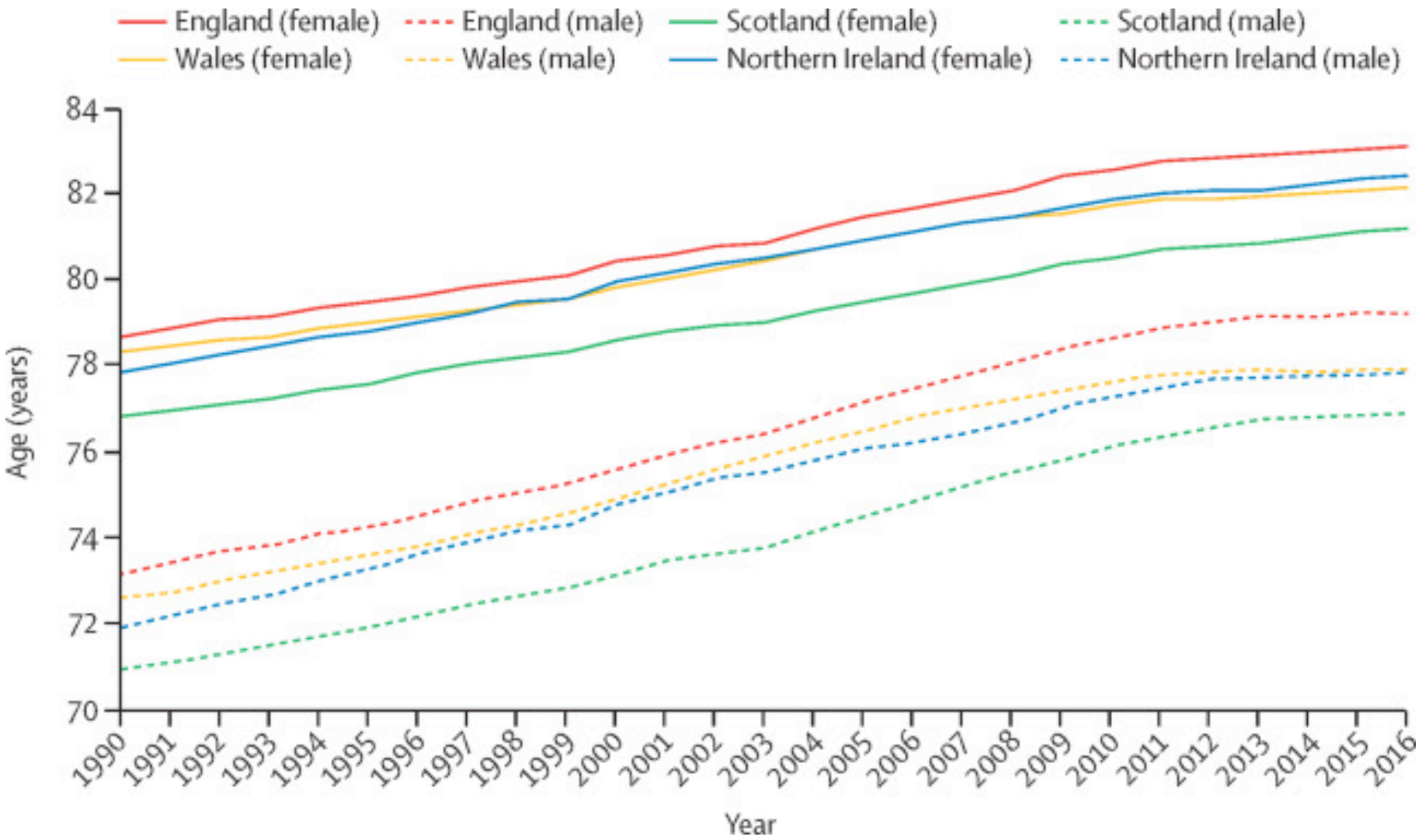
All-cause age-standardised YLL and YLD rates per 100 000 population by UK country and English Upper Tier Local Authorities, 2016

YLLs=years of life lost. YLDs=years lived with disability.

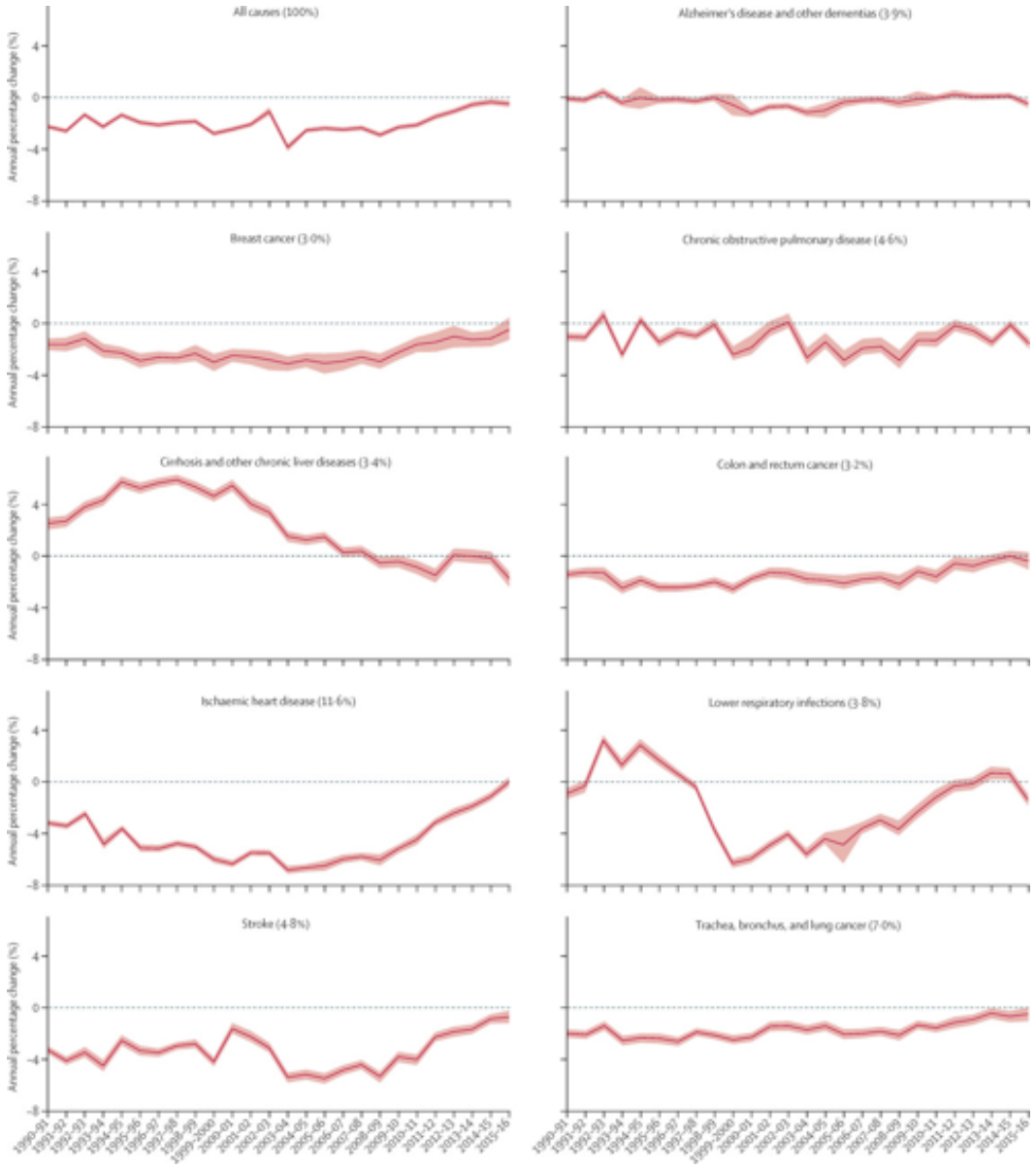


Attributable risk for age-standardised all-cause YLL rate per 100 000 population for nine major risk factors, and UTLA level IMD score, for UTLAs in three regions of England, 2016

YLL=years of life lost. UTLAs=Upper-Tier Local Authorities. IMD=Index of Multiple Deprivation.



Life expectancy at birth for England, Scotland, Wales, and Northern Ireland 1990–2016, by sex



Annual percentage change in YLL rate per 100 000 people for the nine causes with the highest national burden, 1990–2016 in England

Added value of this study

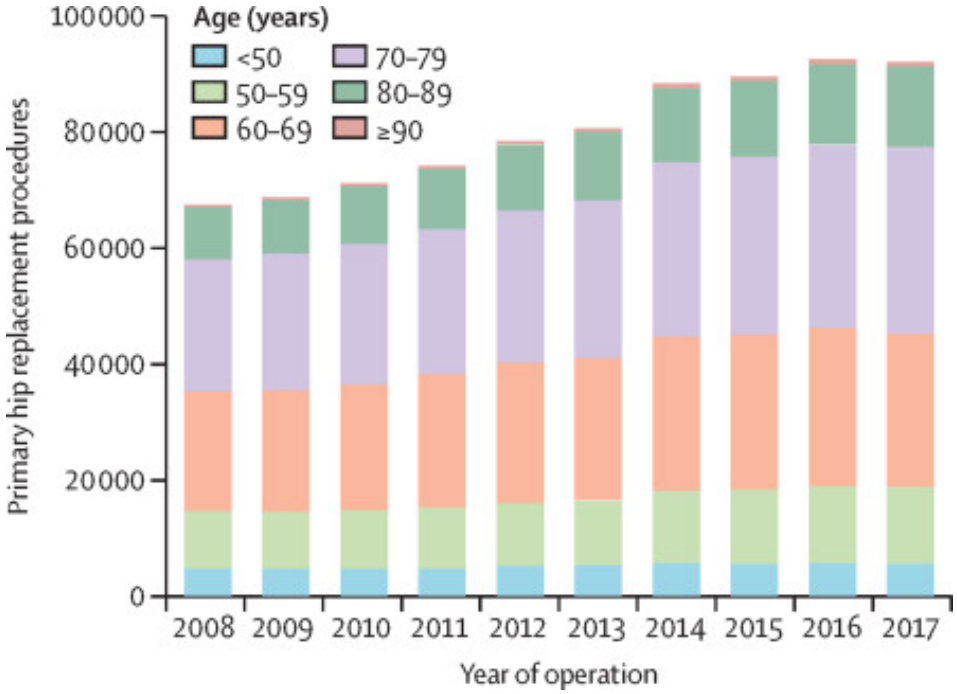
We compare the contributions of individual conditions to years of life lost in the UK for current policy-relevant geographies, the largest contributions being for ischaemic heart disease, lung cancers, cerebrovascular disease, and chronic obstructive pulmonary disease. The extent to which the burden due to these conditions is attributed to specific potentially preventable risks is also quantified (eg, for tobacco use, poor diet, alcohol, obesity, and air pollution). Variation in burden between local areas is described and shown to relate strongly to deprivation. Opportunity to reduce burden due to premature mortality by addressing specific risk factors is also shown to correlate strongly with deprivation. Non-fatal conditions are identified as increasingly important contributors to overall burden across the UK, particularly low back and neck pain, skin diseases, migraine, sense organ diseases, and depressive and anxiety disorders. Updated GBD estimates show that the slowed rate of improvement in overall mortality rates in the UK since 2010 appears to be condition specific and largely driven by decreases in the rate of improvement in mortality from cardiovascular disease and certain cancers.

Implications of all the available evidence

We describe and quantify the extent to which the UK could reduce the overall burden of fatal and non-fatal conditions through effective prevention. The results identify and rank potential local, regional, and national priorities for action that would reduce burden and provide relevant support for local and national advocacy on such priorities. These estimates should directly inform long-term planning for health in the UK—for example, the 10-year plan for the National Health Service in England from 2019. Social and economic determinants of ill health are an overriding concern. There is a need for economic development and regeneration of poorer parts of the country, and for high-quality health improvement programmes and care services in these areas. As mortality continues to reduce, albeit more slowly than before, ill health due to low back pain, skin diseases, sense organ diseases, and depressive disorders makes an increasing contribution to overall burden of disease. Local estimates of ill health that are used to guide policy and practice could be improved and made more comparable by better use of existing data. Health records and linkage to survey data should be used more extensively to refine disease prevalence estimates, improve consistency between GBD and other sources, and provide more reliable data to guide policy and programmes to address these causes of ill health and their sequelae.

Hip replacement

Total hip replacement is a frequently done and highly successful surgical intervention. The procedure is undertaken to relieve pain and improve function in individuals with advanced arthritis of the hip joint. Symptomatic osteoarthritis is the most common indication for surgery. In paper 1 of this Series, we focus on how patient factors should inform the surgical decision-making process. Substantial demands are placed upon modern implants, because patients expect to remain active for longer. We discuss the advances made in implant performance and the developments in perioperative practice that have reduced complications. Assessment of surgery outcomes should include patient-reported outcome measures and implant survival rates that are based on data from joint replacement registries. The high-profile failure of some widely used metal-on-metal prostheses has shown the shortcomings of the existing regulatory framework. We consider how proposed changes to the regulatory framework could influence safety.



Distribution of primary hip replacements by age in England and Wales since 2008

Causation

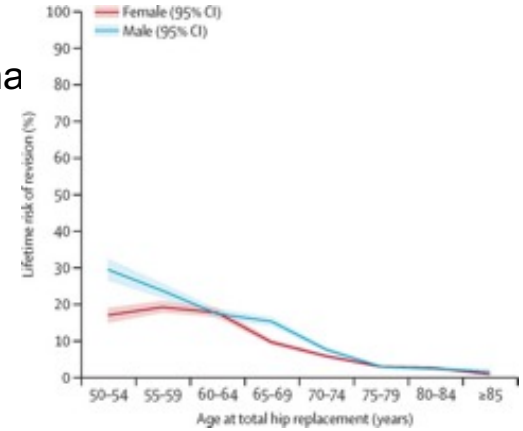
The principal causal indications for total hip replacement are osteoarthritis (which accounted for 90% of procedures in the UK in 2017), fractured neck of femur (5%), avascular necrosis (2%), dysplasia (2%), and inflammatory arthritis (1%). Hip osteoarthritis has multifactorial causes, with biological and mechanical components tha are dictated by genetic and environmental factors. Salient patient-specific risk factors include age, sex, trauma, and joint morphology. Femoroacetabular impingement is increasingly recognised as a cause.[16]

The association of hip osteoarthritis with obesity is much less strong than that of knee osteoarthritis, for reasons that remain unclear. No strong evidence of an association with diet exists. Worldwide, as populations age, the incidence of osteoarthritis is predicted to rise.

The median age at primary total hip replacement in the UK is 69 years (interquartile range 61–76).

The proportion of younger patients undergoing surgery has increased in the USA, and those younger than 65 years are predicted to represent 52% of all patients by 2030. In the UK and Australia, however, the proportion has remained stable: 36% are aged less than 65 years in Australia, and 32% are aged less than 65 years in the UK.

Total hip replacement remains more commonly undertaken in women than in men, with a stable ratio of 1·5:1 in the UK, related to discrepancies in osteoarthritis incidence between men and women.

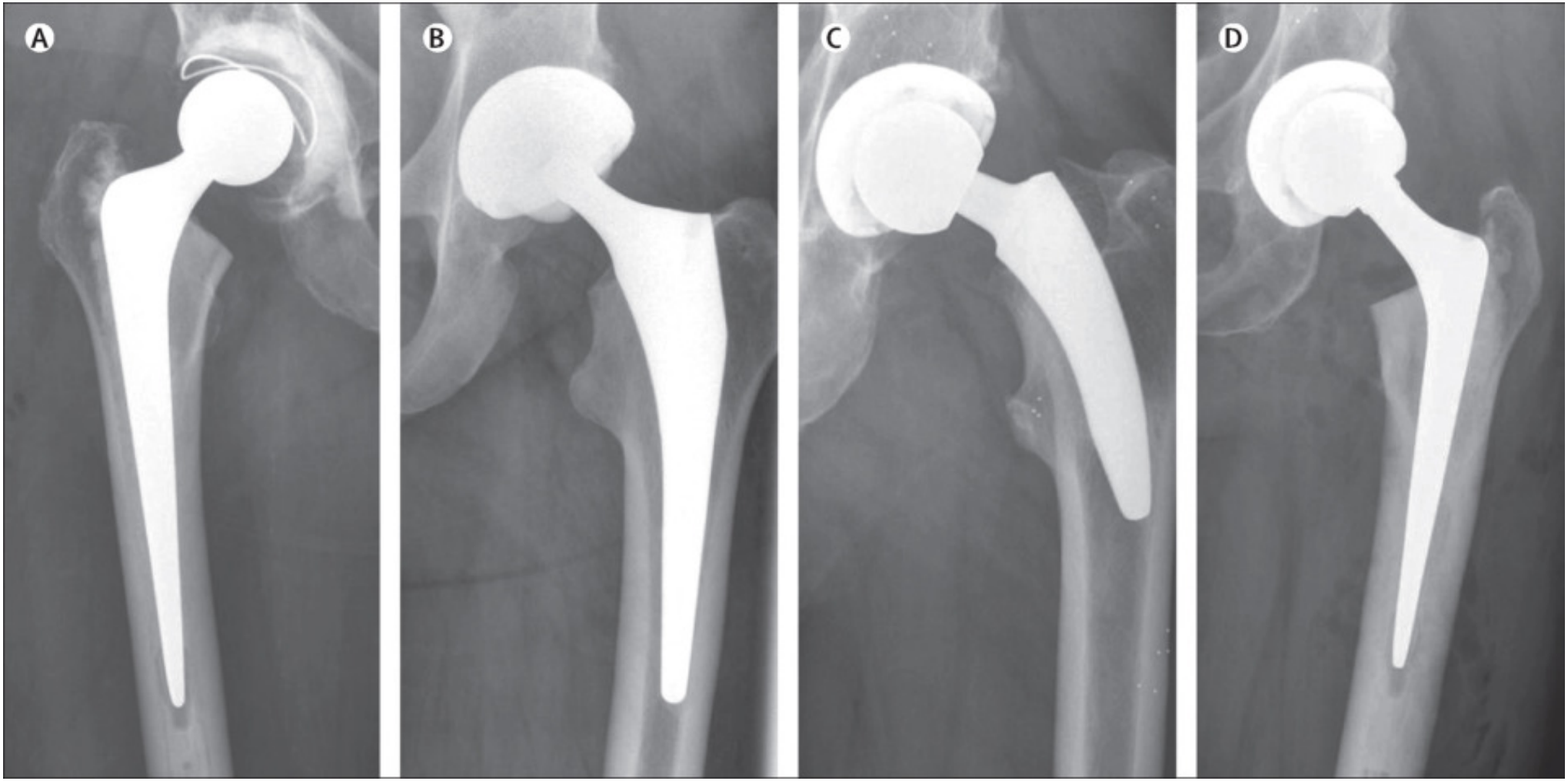


Lifetime risk of revision after total hip replacement

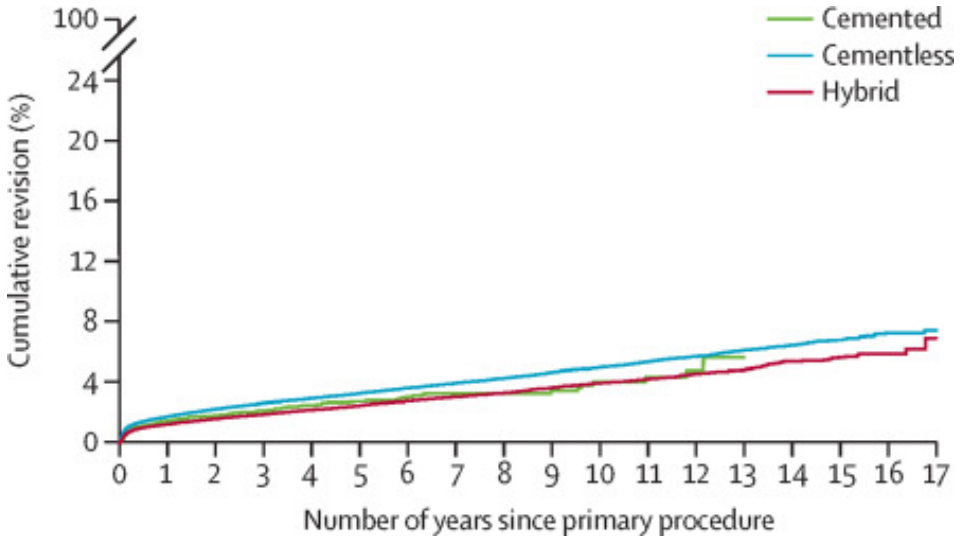
Decision making for surgery

The principal clinical indication for total hip replacement is end-stage arthritis, with joint pain and stiffness that is resistant to non-operative treatments. Non-operative treatments include activity modification, physiotherapy, and oral analgesics.

Symptoms are not reliably associated with the degree of structural disease on imaging, although surgery is rarely indicated in the absence of full-thickness cartilage loss. In patients with atypical hip pain, intra-articular anaesthetic hip injections have been used as a diagnostic aid; however, whether response to injections predicts outcome from hip replacement remains unclear. Intra-articular corticosteroid injections should be discouraged within 3 months before a planned hip replacement because of a potential increase in risk of infection.



Total hip replacement with different implant designs and fixation
Postoperative radiographs of cemented total hip replacement (A); cementless total hip replacement (B), with conventional length femoral stem; cementless total hip replacement, with short length femoral stem (C); and hybrid total hip replacement (D).



Cumulative percentage revision of primary total hip replacement by fixation (primary diagnosis of osteoarthritis)

Regulation and surveillance

In the past 10 years, high-profile litigation cases involving several surgical specialties have been brought in response to the insertion of medical devices with unacceptable complication rates. Investigations following the vaginal mesh and the Poly Implant Prothèse silicone breast implant cases, both of which caused enormous distress to thousands of patients, suggested that the regulatory process governing the introduction of these medical devices was inadequate. Within orthopaedics, the discovery of high failure rates of metal-on-metal hip replacements that had been implanted into a million patients worldwide similarly led to calls to reform the regulatory process.

Benchmarking

NICE advises that only prostheses with rates (projected or actual) of revision of 5% or less at 10 years are implanted outside clinical trials. To supply the NHS with a list of approved prostheses, the Orthopaedic Device Evaluation Panel (ODEP) was created in 2002. The volunteer-led panel considers data on revision rate from manufacturers, registries, and independent studies, and issues a rating for each device. Implants are first rated once 3-year revision rate data have been obtained, with ratings updated at specified time intervals.

Conclusion

Hip replacement remains one of the most effective surgical interventions. This procedure has enabled millions of patients with severe hip pain and functional limitation to regain a high quality of life. Further advances have been made in implant material and design, surgical technique, and perioperative management. Most patients can expect their prosthesis to function without complications for more than 20 years.

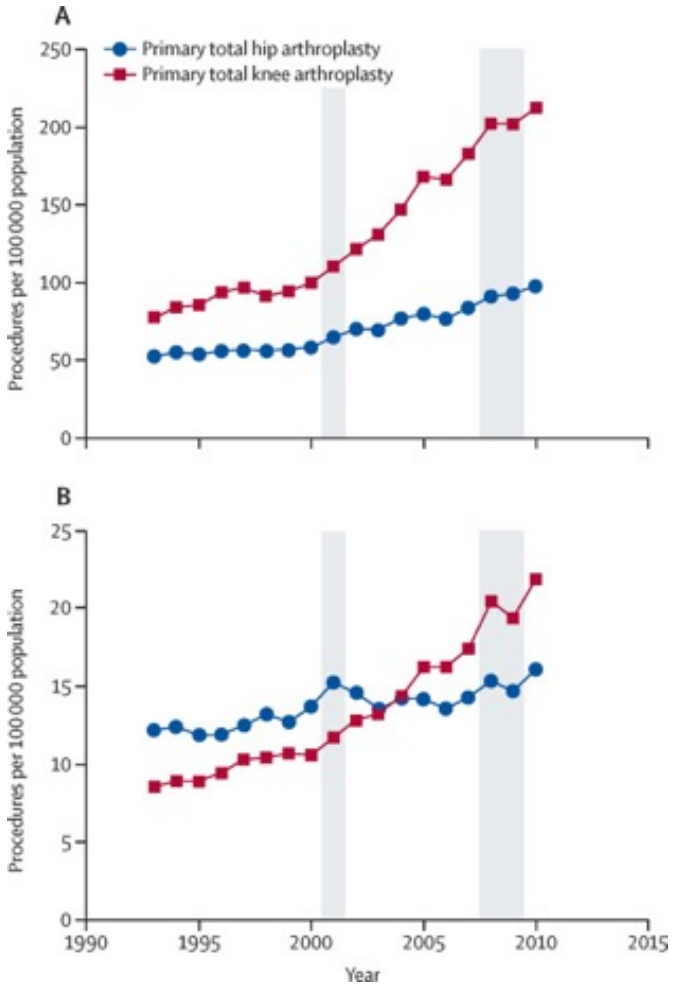
Knee replacement

Summary

Knee replacement surgery is one of the most commonly done and cost-effective musculoskeletal surgical procedures. The numbers of cases done continue to grow worldwide, with substantial variation in utilisation rates across regions and countries. The main indication for surgery remains painful knee osteoarthritis with reduced function and quality of life. The threshold for intervention is not well defined, and is influenced by many factors including patient and surgeon preference. Most patients have a very good clinical outcome after knee replacement, but multiple studies have reported that 20% or more of patients do not. So despite excellent long-term survivorship, more work is required to enhance this procedure and development is rightly focused on increasing the proportion of patients who have successful pain relief after surgery. Changing implant design has historically been a target for improving outcome, but there is greater recognition that improvements can be achieved by better implantation methods, avoiding complications, and improving perioperative care for patients, such as enhanced recovery programmes. New technologies are likely to advance future knee replacement care further, but their introduction must be regulated and monitored with greater rigour to ensure patient safety.

Epidemiology of knee replacement

The use of knee replacement as a treatment for arthritis continues to increase. In the UK, more than 100 000 knee replacements are now done each year and a similar pattern of increased frequency is reported by many worldwide joint registries. Total numbers of procedures in the USA have now reached 700 000 per year, and the number is increasing as predicted despite periods of economic downturn. Projected analyses from different counties all suggest that, even with conservative estimates, the increased use of knee replacement will continue.



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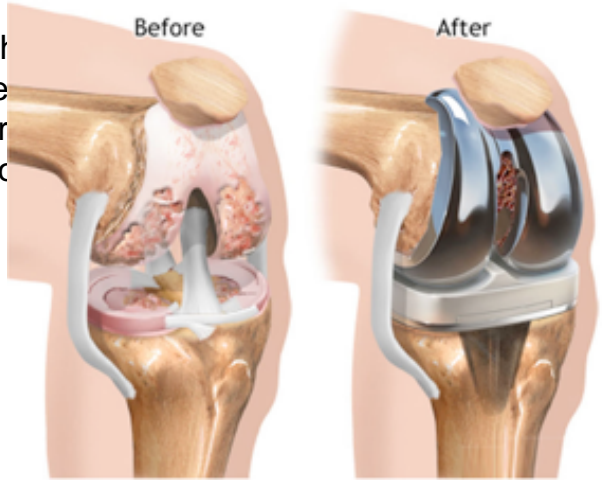
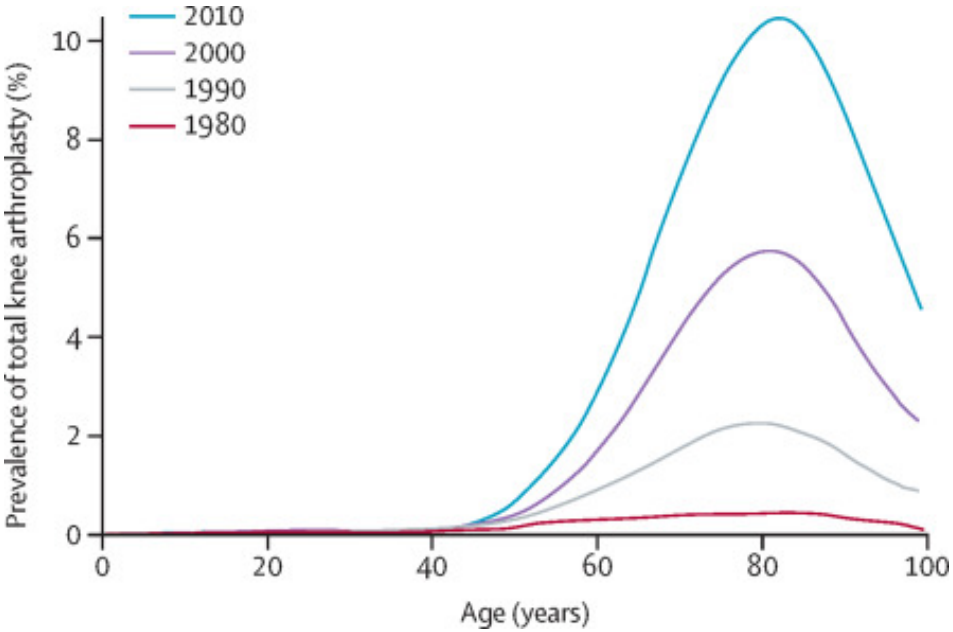
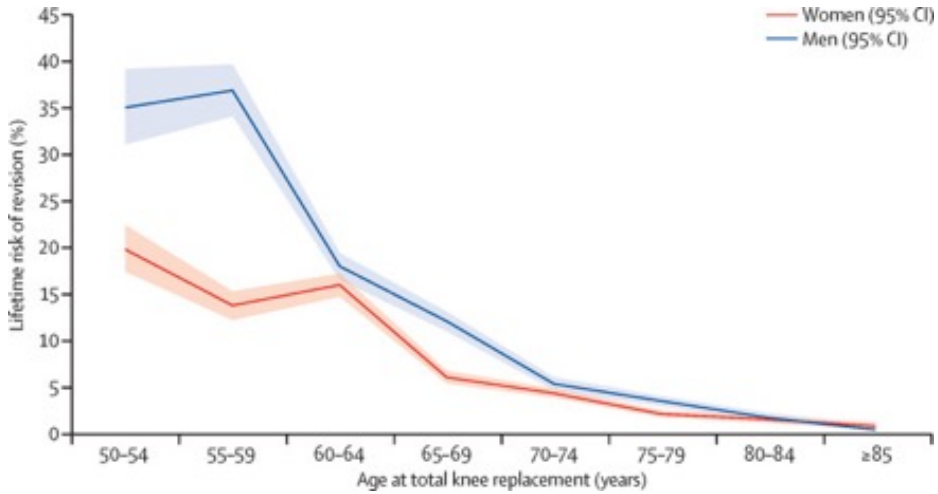


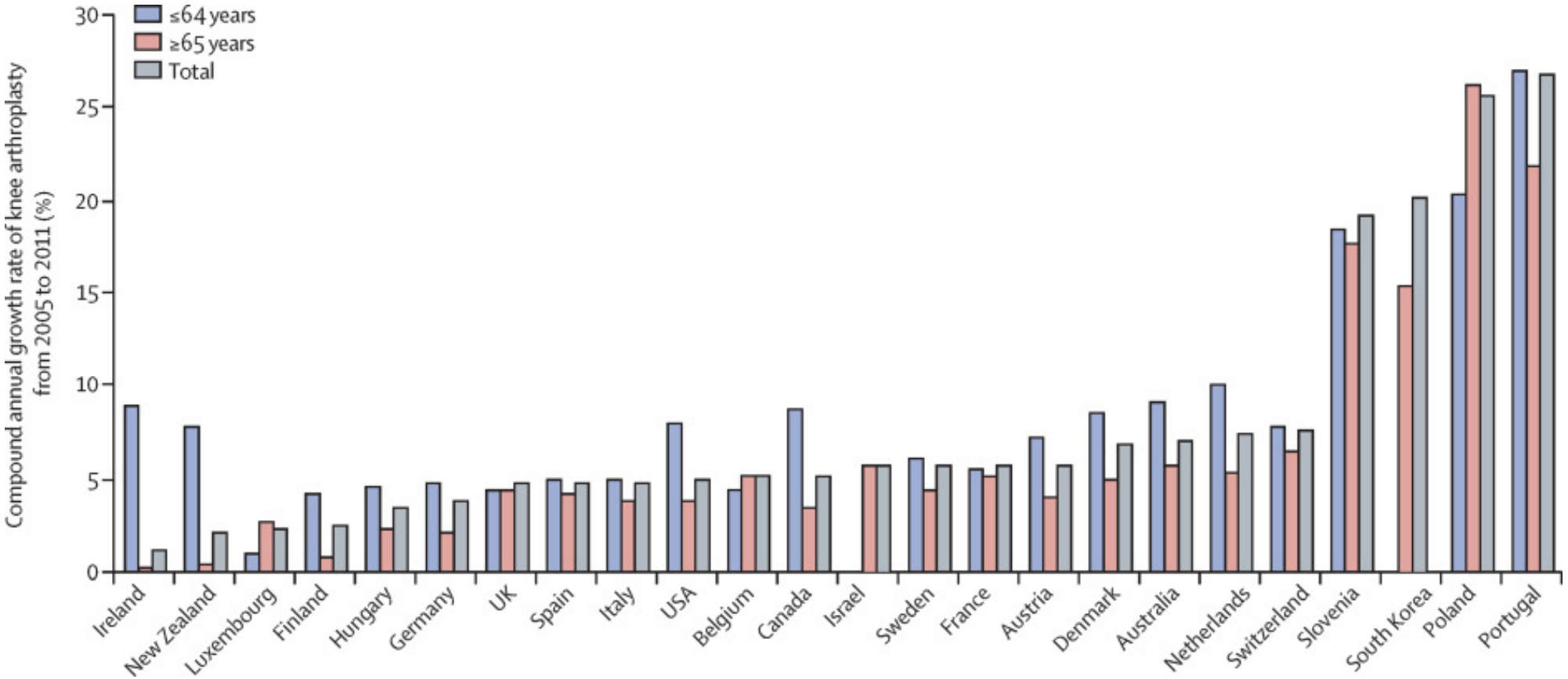


Secular changes in the prevalence of total knee arthroplasty in the total US population between 1980 and 2010



Lifetime risk of revision after total knee replacement

The plot shows the estimates of lifetime risk of total knee replacement revision against age at the time of primary total knee replacement surgery in 5-year age bands, and is stratified by sex. Shaded areas are 95% CIs. Results are adjusted for lost and censored population.



Growth rates in knee arthroplasty among OECD countries

Indications for knee replacement surgery

Total knee replacement has traditionally been offered to older patients with intolerable knee pain, unacceptable activity limitation with the loss of highly valued activities, and severe end-stage osteoarthritis of the joint. Historically, arthroplasty surgeons have been reluctant to operate on patients with either morbid obesity (because of the higher risk of perioperative complications), and on patients younger than 55 years (because of the increased likelihood of revision in their lifetime).

Surgeons have similarly been cautious about operating on patients with serious medical comorbidities, again for fear of complications but also on those with widespread pain and or catastrophising behaviour, because these problems are associated with higher risk of persistent pain. Finally, surgeons have historically set high levels of preoperative pain and functional limitation to justify the risk of surgical intervention.

Recent studies support expanding these traditional indications. For example, although morbid obesity is indeed associated with greater risk of perioperative complications, such as postoperative infection, recent studies show that individuals with a body-mass index (BMI) of more than 35, and even more than 40, experience similar pain relief as patients who are not obese.

An important contributor to the contemporary broadening of indications of knee replacement is the growing importance of the patient's voice in decisions about whether to undertake surgery. Clinical guidance from the UK National Institute for Health and Care Excellence and the American Academy of Orthopaedic Surgeons, together with other authoritative bodies, emphasise the importance of engaging patients in shared decision-making conversations about whether to undertake knee replacement. Shared decision making involves patients being appraised of the short-term and long-term risks and benefits of operative and non-operative therapy, to enable a decision that is consistent with their preferences and values. Knee replacement is only one option for patients with advanced knee osteoarthritis, and patients should be informed of alternatives.

For example, physical therapy programmes of strengthening and neuromuscular training can give symptomatic improvement in two-thirds of patients with advanced knee osteoarthritis. In this shared decision-making model, the patient and not the physician has the ultimate say over whether to proceed with surgery or not, based on their own individual assessment of the balance of risk versus capacity to benefit.

- Panel

The top ten priority research areas for knee replacement surgery for osteoarthritis

1 What are the most important patient and clinical outcomes in knee replacement surgery for people with osteoarthritis, and what is the best way to measure them?

2 What is the optimal timing for hip and knee replacement surgery for best postoperative outcomes?

3 What are the preoperative predictors of postoperative success, and what are the risk factors of poor outcomes?

4 What preoperative, intraoperative, and postoperative factors can be modified to influence outcome following knee replacement?

5 What is the best pain control regimen preoperatively, perioperatively, and immediately after surgery?

6 What are the best techniques to control for long-term chronic pain and improve long-term function following knee replacement?

7 What are the long-term outcomes of non-surgical treatments compared with operative treatment for patients with advanced knee osteoarthritis?

8 What is the most effective preoperative and postoperative patient education support and advice for improving outcomes and satisfaction for people following knee replacement?

9 What is an ideal postoperative follow-up period and the best long-term care model for people with osteoarthritis that have had knee replacement?

10 What is the best way to protect patients from the risk of thrombotic events associated with knee replacement?

Adapted from James Lind Alliance Priority Setting Partnership.[31]

Development and new technology in knee replacement surgery

Design of total condylar knee replacement

Posterior cruciate retaining or sacrificing total condylar knee designs remain the two most widely used total knee replacement options. Incremental design development continues, such as gender-specific and high-flex components, but evidence that these changes in component shape produce any meaningful improvement in outcome is sparse. Most knee replacements still use a metal on polyethylene-bearing surface and polyethylene wear remains a major cause of implant failure. Around 20 years ago, highly cross-linked polyethylene, so-called second-generation polyethylene, was introduced and has been successful in minimising polyethylene wear; thereby reducing aseptic loosening and revision. More recently, vitamin-E-infused, highly cross-linked polyethylene, so-called third-generation or antioxidant polyethylene has been developed, but the efficacy of this polyethylene remains to be established.

Alignment in total knee replacement

For more than 30 years, the standard approach to implanting total knee replacements has been to aim for mechanical alignment, where the hip, centre of the reconstructed knee, and the ankle are in alignment. More recently, kinematic alignment has been proposed as an alternative implantation strategy, aiming to mimic the predisease joint surface orientation. This procedure is thought to optimise ligament balance and knee kinematics without the need for ligament releases. The global experience with kinematic alignment in total knee replacement is limited, but a recent literature review reported more favourable outcome after kinematically aligned total knee replacement compared with mechanical alignment; however, the improvement is not universal. The benefit from different alignment methods is possibly influenced by the pattern of osteoarthritis for each individual patient. Mechanical alignment remains the mostly widely used method of implantation and further investigation of the safety of kinematic alignment is needed before the technique can be considered for widespread use.

Conclusion

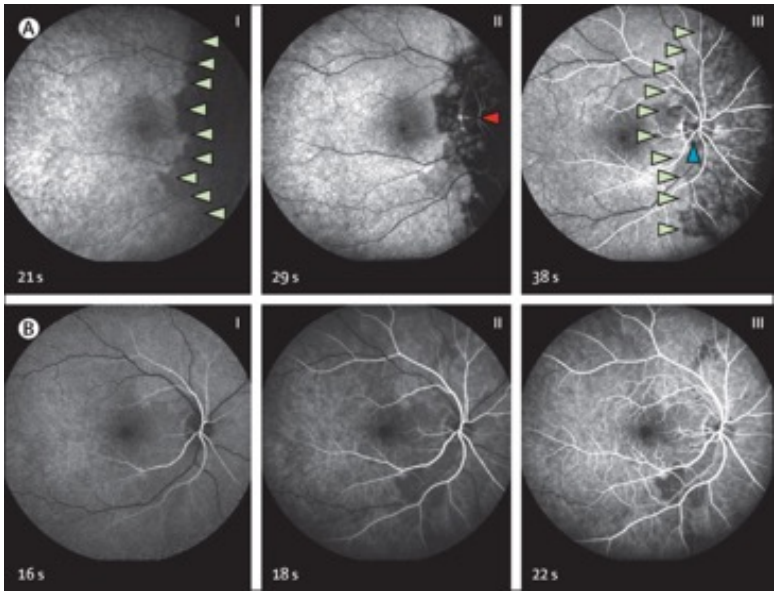
Knee replacement surgery is a highly successful established technology, with good evidence of successful treatment outcome and long-term implant survival. A proportion of patients continue to have poor results and addressing this issue is the major challenge for improving care, particularly given the continued increase in worldwide usage and the increasing numbers of younger patients undergoing surgery. Continued incremental changes in implant design do not appear to have achieved any substantial improvement in outcome for patients, and focus could shift towards optimising modifiable patient factors and the use of alternatives to total knee replacement, such as partial knee replacement and perioperative management.

The field's understanding of patient-reported outcome of knee replacement has advanced, but it still needs further refinement. National registries continue to enable our understanding of knee replacement and new analysis methodologies must be harnessed to maximise benefit. As with all medical areas, new technology is being developed at an increasing rate and modernising regulatory change will help assessment of implants and devices to maintain patient safety. Given the existing success of established knee replacement technology, more creative assessment methodologies, including more randomised controlled trials and adaptive designs, must be used when introducing new devices. Greater focus on patient involvement and maintaining patient safety in this process will help to ensure knee replacement continues to be one of the most successful surgical procedures in modern medicine.

Amaurosis fugax

The differential diagnosis of transient monocular vision loss (TMVL), based on clinical history alone, is a common clinical problem. A 66-year-old man presented with a 3-month history of recurrent right TMVL. He had more than 15 episodes without provocation. He described multiple islands of visual loss that coalesced to complete monocular blindness—persisting for several minutes—followed by recovery in a reverse manner. While venous access was being obtained for fluorescein angiography (FA), the patient reported onset of an attack. The examination was thus fortuitously done during vision loss.

Normally, following intravenous injection, the dye passes through the short posterior ciliary arteries and appears in the optic disc and choroid within 8–12 s, depending on the age, cardiovascular status of the patient, and speed of dye injection. The arterial retinal circulation appears 11–18 s after injection. However, in our patient, FA of the right eye showed slightly delayed filling of the central retinal artery and severely delayed filling of the nasal choroid and prelaminar region of the optic disc. The circulation of the left eye was normal. Examination 1 week later confirmed retinal circulation was normal between attacks. A diagnosis of vasospasm was made and after treatment with nifedipine 5 mg twice a day, the attacks ceased. The patient remained attack free at 8 months' follow-up. Right place, right time: fluorescein angiography during transient monocular visual loss



(A) First row shows fluorescein angiograms of the right eye during reticulated pattern transient monocular vision loss at (I) 21 s after injection—normal filling limited to the temporal part of the choroid (green arrows); (II) 29 s after injection—beginning of the filling of the retinal arteries (red arrow), and no filling of the nasal choroid and of the whole prelaminar region of the optic disc; and (III) 38 s after injection—beginning of the nasal choroidal filling (green arrows) and of the prelaminar region of the optic disc (blue arrow). (B) Second row shows fluorescein angiograms of the right eye 1 week after the recorded attack (I) 16 s and (II) 18 s after injection—normal filling of the choroid, retinal arteries, and prelaminar region of the optic disc; and (III) 22 s after injection—filling of the retinal veins.

Unter einer Amaurosis fugax versteht man eine vorübergehende Sehstörung, die durch Durchblutungsstörungen der Netzhautgefäße entsteht.
Ursächlich ist meist ein plötzlich auftretender unilateraler Verschluss der Arteria centralis retinae(Netzhautischämie) mit einem anschließenden schmerzlosen Visusverlust.
Häufige Ursachen sind:
Arteriosklerose (V. a. Stenose und Plaquebildung der Arteria carotis interna)
Kardiale sowie paradoxe Thrombembolien
Vaskulitiden: Arteriitis temporalis, Panarteriitis nodosa
Vasospasmus

Die Amaurosis fugax ist prinzipiell selbstlimitierend. Jedoch sollte sie als Warnsignal der zugrundeliegenden Erkrankung betrachtet werden. Es sollte unbedingt eine weiterführende Diagnostik (Dopplersonographie, Echokardiographie, Rheumaserologie) durchgeführt werden.
Im Falle einer bekannten Arteriitis temporalis muss umgehend eine Prednisolon-Stoßtherapiebegonnen werden, um eine dauerhafte Blindheit zu vermeiden.

Many attempts have been made to classify TMVL from patients' descriptions to distinguish embolic from non-embolic attacks. Further, it has been speculated that the reticulated, patchy pattern of TMVL corresponds to interruption of the choroidal circulation—related to its lobular arrangement. This will very rarely occur due to thromboembolism because of the extensive anastomoses between the posterior ciliary arteries supplying the choroid. However, whereas vasospasm of the central retinal artery has been directly observed, choroidal perfusion abnormalities can usually only be identified by FA, and no photographic evidence for this assertion has been published. Our Clinical Picture provides the first direct confirmation for the proposed theory that the reticulated pattern of TMVL is a signature of transient ischaemia of the choroidal lobular circulation. Clearly, such cases should be managed as vasospasm.